PAGE 2018 PROGRAM and ABSTRACTS

Tuesday 29 May			
14:00-18:00	**Registration at the Conference Venue**		
18:30-21:30	**Opening ceremony, welcome reception and dinner**		
Wednesday 30 May			
08:00-08:45	**Registration**		
08:45-09:00	**Welcome and Introduction**		
09:00-10:10	**Model-based dose individualisation – biomarker focus**		*Chair: Chantal Csajka, Nick Holford*
09:00-09:20	*Thierry Buclin*	Meeting clinicians' and patients' needs in the practice of therapeutic monitoring	
09:20-09:50	*Catherine Sherwin*	Model-based dose individualization approaches using biomarkers	
09:50-10:10	*Ron Keizer*	Experiences in applied clinical pharmacometrics: challenges, recommendations, and research opportunities	
10:10-11:40	**Coffee break, Poster and Software session I**		
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter		
11:40-12:20	**Model-based dose individualisation – biomarker focus, continued**		*Chair: Chantal Csajka, Nick Holford*
11:40-12:00	*Maddalena Centanni*	A pharmacometric framework for dose individualisation of sunitinib in GIST	
12:00-12:20	*Chloé Pasin*	Use of mathematical modeling for optimizing and adapting immunotherapy protocols in HIV-infected patients	
12:20-13:00	**Estimands**		*Chair: France Mentré*
12:20-12:35	*Mouna Akacha*	Background on estimands and why are they important?	
12:35-12:50	*Mick Looby*	PMX perspective on estimands	
12:50-13:00		Discussion on estimands	

13:00-14:30	**Lunch**		
14:30-15:50	**Stuart Beal Methodology Session**		*Chair: Justin Wilkins*
14:30-14:50	*Camille Vong*	Power assessment for hierarchical combination endpoints using joint modelling of repeated time-to-event and time-to-event models versus Finkelstein-Schoenfeld method	
14:50-15:10	*Yixuan Zou*	A novel score test-based method for efficient covariate selection in population pharmacokinetic analysis	
15:10-15:30	*Qing Xi Ooi*	Evaluation of assumptions underpinning pharmacometric models	
15:30-15:50	*Mats Karlsson*	Extensive and automatic assumption assessment of pharmacometric models	
15:50-17:20	**Tea break, Poster and Software session II**		
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter		
17:20-17:40	**Clinical applications**		*Chair: Marylore Chenel*
17:20-17:40	*Oskar Alskär*	An integrated glucose homeostasis model of glucose, insulin, C-peptide, GLP-1, GIP and glucagon in healthy subjects and patients with Type 2 diabetes	
17:40-18:00	**Pharmacoeconomics**		*Chair: Marylore Chenel*
17:40-18:00	*Daniel Hill-McManus*	Application of a linked pharmacometric/pharmacoeconomic model to assess the impact of non-adherence: Application to the treatment of gout	

Thursday 31 May

08:30-09:55	**Lewis Sheiner Student Session**		*Chair: Julie Bertrand, Alain Munafo, Ana Ruiz*
08:30-08:50	*Simon Buatois*	A pharmacometric extension of MCP-MOD in dose finding studies	
08:50-09:10	*Benjamin Guiastrennec*	New dosing recommendations for anti-tuberculosis therapy in Indian children	
09:10-09:30	*Jurgen Langenhorst*	Cause-specific hazard models with Markovian elements to quantify the fludarabine exposure-response relationship: from learning to confirming in allogeneic hematopoietic cell transplantation	
09:30-09:50	*Gustaf Wellhagen*	A bounded integer model for rating and composite scale data	
09.50-09.55	**Presentation of Lewis Sheiner student session awards**		

09:55-11:30	**Coffee break, Poster and Software session III**		
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter		
11:30-12:30	**Oncology**		*Chair: Lena Friberg*
11:30-11:50	*Phyllis Chan*	Assessment of a model to correlate early tumor size response to overall survival in relapsed or refractory diffuse large B cell lymphoma patients	
11:50-12:10	*Rui Zhu*	Exposure-response (E-R)-based product-profile (PP)-driven clinical utility index (CUI) to support phase III dose selection in oncology	
12:10-12:30	*Zinnia Parra-Guillen*	A quantitative modelling framework to inform dose selection of Xentuzumab, a dual insulin-like growth factor-I/II neutralizing antibody in cancer patients	
12:30-12:35	**Announcement for ACoP9 (2018)**		*CJ Musante*
12:35-14:10	**Lunch**		
14:10-15:10	**Immuno-oncology**		*Chair: Dinesh de Alwis, Pascal Girard*
14:10-14:40	*Scott K Pruitt*	Clinical overview of immunotherapy in oncology	
14:40-15:10	*Benjamin Ribba*	Drug response variability and optimal dosing in immuno-oncology	
15:10-16:40	**Tea break, Poster and Software session IV**		
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter		
16:40-17:20	**Immuno-oncology, continued**		*Chair: Dinesh de Alwis, Pascal Girard*
16:40-17:00	*Rukmini Kumar*	Predicting response and identifying responders to combination cancer immunotherapy in melanoma using Quantitative Systems Pharmacology (QSP) models	
17:00-17:20	*Hanna Silber Baumann*	PKPD analysis of soluble CD25 to characterize the concentration-effect relationship observed following the administration of Cergutuzumab Amunaleukin, a targeted immunocytokine for cancer immunotherapy	
17:20-17:25	**Announcement for WCoP 2020**		*Stacey Tannenbaum*
18:30-01:30	**Social event**		

Friday 1 June			
09:15-09:55	**Clinical Applications**		*Chair: Marylore Chenel*
09:15-09:35	*David Ternant*	Population and Bayesian kinetic modelling of necrosis biomarkers to assess the effect of conditioning therapies on infarct size	
09:35-09:55	*João Abrantes*	Integrated modelling of factor VIII activity kinetics, occurrence of bleeds and individual characteristics in haemophilia A patients using a full random effects modelling approach (FREM)	
09:55-10:35	**Systems pharmacology**		*Chair: Charlotte Kloft*
09:55-10:15	*Chihiro Hasegawa*	Simplification of multi-scale systems models for data-driven analyses: what has progressed in these 5 years?	
10:15:10:35	*Elin Boger*	A partial differential equation approach to inhalation PBPK modelling	
10.35-10.40	**Preview of PAGE 2019**		
10:40-11:20	**Coffee break and Software session**		
11:20-11:30	**DDMoRe Model Repository challenge – prize ceremony**		*Chair: Thomas Dorlo, Céline Sarr*
11:30-12:10	**Antivirals**		*Chair: Thomas Dorlo*
11:30-11:50	*Sulav Duwal*	A multiscale mechanistic framework to predict drug-class specific prophylactic efficacy of antiviral drugs against HIV	
11:50-12:10	*Vincent Madelain*	Ebola viral dynamics in nonhuman primates: insights into virus immuno-pathogenesis and antiviral strategies	
12.10-12.20	**Closing remarks**		
12:20-12:35	**Audience input for potential PAGE2019 topics**		

B-03: *Thierry Buclin* Meeting clinicians' and patients' needs in the practice of therapeutic monitoring

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Objectives:

- To heighten awareness of the clinical importance of Pharmacometrics for elaborating efficient strategies of treatment individualization at the patient's level through therapeutic monitoring – an underappreciated aspect of Precision Medicine;
- To outline a structured overview of how healthcare providers can interpret and draw the best benefit from therapeutic monitoring tests, namely either drug concentration or biomarker measurement results;
- To draw attention onto the inexorable advances in point-of-care monitoring technologies and connected decision support systems that are currently redesigning therapeutic practices.

Overview/Description of presentation:

We will revisit the development of therapeutic concentration monitoring for imatinib, the archetypal targeted anticancer agent, whose story might apply with few changes to manifold drugs. The phases of this development roughly parallel the cognitive steps to follow during the interpretation of a monitoring result:

1. Population PK studies are instrumental to quantify and to partly explain the variability in concentration exposure under standard dosage. Ideally aggregated in a meta-analysis [1], they bring an answer to the question of "**normality**" or expectedness of a concentration result in a given patient, which is well illustrated using *a priori* prediction percentiles.
2. PKPD studies [2] contribute to clarify the issue of optimal level of exposure and to answer the question of "**suitability**" or appropriateness of a concentration result, usually summarized through target ranges (either population or individualized).
3. Population PKPD modeling enables Bayesian adaptation [3] to devise proper dosage **adjustment** based on concentration results, and need to re-monitor; *a posteriori* maximum likelihood trajectory with prediction percentiles is ideally suited to graphically present this information.
4. Clinical evidence of usefulness is required for any monitoring tool whatever its technical merits. Confirmation trials in therapeutic monitoring raise specific challenges [4] but bring the last word to the question of the **indication** to use the corresponding test in medical practice.

Conclusions/Take home message:

Pharmacometric approaches are now deeply integrated in the clinical development of medicinal drugs. Still in many instances, they have failed to provide physicians and patients with optimal directions for prescription individualization, in particular when therapeutic monitoring tests, based on either concentrations or biomarkers measurement, could have been anticipated to optimize a drug's clinical benefit [5]. The usually unfavourable position of decision makers in pharmaceutical companies towards therapeutic monitoring is not the only explanation for this situation [6]. It also results from a relative lack of convenient monitoring tests readily accessible at the point of care, of user-friendly interpretation tools, of

evidence-based supporting data and of general monitoring culture among healthcare providers [7]. Fortunately, progress is underway and the appraisal of possibilities offered by therapeutic monitoring is due to improve and to become systematic. The pharmacometrics community will hopefully take the responsibilities and the leadership that such developments need.

References:

[1] Gotta V, Buclin T, Csajka C, Widmer N. Systematic review of population pharmacokinetic analyses of imatinib and relationships with treatment outcomes. Ther Drug Monit. 2013;35(2):150-67.
[2] Gotta V, Bouchet S, Widmer N, Schuld P, Decosterd LA, Buclin T, Mahon FX, Csajka C, Molimard M. Large-scale imatinib dose-concentration-effect study in CML patients under routine care conditions. Leuk Res. 2014;38(7):764-72.
[3] Gotta V, Widmer N, Montemurro M, Leyvraz S, Haouala A, Decosterd LA, Csajka C, Buclin T. Therapeutic drug monitoring of imatinib: Bayesian and alternative methods to predict trough levels. Clin Pharmacokinet. 2012;51(3):187-201.
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[5] Holford NH, Buclin T. Safe and effective variability-a criterion for dose individualization. Ther Drug Monit. 2012;34(5):565-8.
[6] Buclin T, Widmer N, Biollaz J, Decosterd LA. Who is in charge of assessing therapeutic drug monitoring? The case of imatinib. Lancet Oncol. 2011;12(1):9-11.
[7] Buclin T, Gotta V, Fuchs A, Widmer N, Aronson J. Monitoring drug therapy. Br J Clin Pharmacol. 2012;73(6):917-23.

B-04: *Catherine Sherwin* Model-based Dose Individualization Approaches Using Biomarkers

Venkata Yellepeddi, Catherine M. Sherwin
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Objectives: This presentation aims at describing how modeling framework incorporating biomarker data can be a valuable tool for dose individualization in various diseases. Information on specific models of drugs such as sunitinib, warfarin, sitagliptin, etc. with corresponding biomarker data will be discussed in detail.

Overview/Description of presentation: Biomarkers are helpful in clinical practice as a diagnostic tool, surrogate endpoint to assess clinical safety and efficacy, and for dose individualization. By incorporating complete time-course of biomarker changes in a model, we can quantitatively characterize the link between exposure, biomarker concentrations, and clinical outcome. An established relationship, therefore, may be used for prediction of changes in biomarker concentration and the resulting clinical outcome under a variety of conditions to evaluate individualized dosing approaches. Several examples are available on how model-based analyses of biomarker data can support the dose individualization approach in various disease states. A model relating exposure of anticancer drug sunitinib, biomarkers (vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor (sVEGFR)-2, -3, soluble stem cell factor receptor (sKIT)), and tumor growth to overall survival (OS) was developed to be used for dose individualization to maximize OS [1]. A KPD model that describes the relationship between warfarin dose and international normalized ratio (INR) response was developed. The model can be used to manage *a priori* and *a posteriori* individualization of warfarin therapy in both adults and children [2]. Prostaglandin E2 (PGE_2) levels and thromboxane A2 (TXA_2) inhibition were utilized as biomarkers for developing a model to predict drug effects and select efficacious doses in humans [3]. The key steps in the development of a model incorporating biomarkers are: 1) Development of a population model that describes the PKPD relationship of the drug and identify and quantify important predictors for *a priori* dose individualization 2) Transfer the model to a user-friendly decision support tool for *a priori* and *a posteriori* predictions of drug dose and biomarkers response 3) Optimize performance of model using clinical data.

Conclusions/Take home message: The models discussed in the presentation serve as examples of how pharmacometrics can be used to assess exposure-biomarker-adverse effects-and clinical outcomes relationship in an integrated manner. These models also provide suitable platforms for dose individualization approaches due to their ability to predict clinical outcomes based on biomarker information.

References:

[1] Hansson EK, Amantea MA, Westwood P, Milligan PA, Houk BE, French J, Karlsson MO, Friberg LE. PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3, and sKIT as Predictors of Tumor Dynamics and Overall Survival Following Sunitinib Treatment in GIST. CPT Pharmacometrics Syst Pharmacol. 2013 Nov 20;2:e84.
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B-05: *Ron Keizer* Experiences in applied clinical pharmacometrics: challenges, recommendations, and research opportunities

Ron Keizer, Ranvir Mangat, Srijib Goswami
InsightRX

Background: Pharmacometric research has produced a wealth of advanced modeling techniques and models that could be applied in clinical practice for model-informed precision dosing (MIPD) at the point-of-care. However, while pharmacometrics has gained a stronghold in drug development, the adoption and implementation of MIPD into clinical practice at the point of care is still remarkably low[1]. Arguably, the low uptake of MIPD has been hampered primarily by the lack of easy-to-use user interfaces and connections to electronic hospital records (EHR). Many scientific questions relevant for the effective translation of pharmacometric research into clinical decision support (CDS) tools do however still remain. An overview is presented here of practical challenges, recommendations, and opportunities for future research to optimizing the translation of pharmacometric knowledge into MIPD/CDS solutions.

Methods: Experiences from three years of developing and implementing MIPD/CDS tools into multiple hospitals and for various drug classes (antibiotics and chemotherapeutics) were collected, summarized, and used to identify knowledge gaps in pharmacometric research. Recommendations and potential solutions are presented for each gap.

Results: Challenges and gaps were identified in the following areas:

1. Model selection: the identification of optimal models and clinical validation of models for a specific population is challenging and laborious but a necessary step for effective and safe translation. It is highly recommended that predictive power of the intended model(s) is evaluated before implementation in any new population or new clinical setting, and continuously monitored afterwards. Dedicated diagnostic tools should be developed to support this.
2. Model updating: data collected by the MIPD tool provides insight into the predictive ability of the used models, but should also be used to update the model priors and/or model structure afterwards. (Semi-)automated updating of models and priors to better match a specific population is a largely unstudied area in pharmacometrics but could have large potential.
3. Curation of EHR data: dosing and biomarker data imported from the EHR will inherently contain errors, missing data, and outliers. Algorithms can be developed and employed to filter and cleanse such data, although manual curation is still often necessary to extract optimal use.
4. Handling of outlier patients: both parametric (e.g. flattening of priors) and non-parametric (e.g. extended grid) approaches allow outlier patients to be better captured by a model, although such strategies can be subjective and ad hoc. Retrospective and prospective evaluation of such strategies is highly recommended.
5. Handling of interoccasion variability (IOV): while IOV is almost always relevant in the clinical setting and prone to induce bias if neglected [1], population PK models presented in literature do not always include IOV. Simulation studies indicate that use of individual estimates specific to a previous occasion lead to reduced predictive power in forecasting future exposure [2]. Selective weighting of more recent data points could reduce bias and improve predictive power. Strategies for handling IOV should be studied in analyses of retrospective datasets as simulation studies are necessarily limited by their assumptions.

6. Use of historical data in individualized treatment: long term data may be available for a subject, possibly from multiple prior hospital visits. Incorporation of down-weighted historical data likely provides better predictive ability than neglecting or fully weighting them.
7. Exposure-outcome relationships: while TDM software historically has focused on optimizing drug exposure (or pharmacodynamic measures), linking drug exposure to outcome should be the ultimate aim and will spur adoption of MIPD tools based on clinical and pharmacoeconomic considerations. Such links are currently sparse but can often be studied from routinely collected clinical data.

Conclusions: Challenges and knowledge gaps were identified regarding the optimal implementation population PK/PD models into MIPD/CDS solutions. Some gaps can be addressed by simulation studies or retrospective analysis of large retrospective datasets, while others will require dedicated prospective trials.

References:

[1] Darwich AS et al. Clin Pharmacol Ther. 2017 May;101(5):646-656
[2] Karlsson, MO & Sheiner, LB. J Pharmacokinet Biopharm. 1993 Dec;21(6):735-50.
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B-07: *Maddalena Centanni* A pharmacometric framework for dose individualisation of sunitinib in GIST

M. Centanni, S.M. Krishnan, L.E. Friberg
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Objectives: The rise of targeted cancer therapies has revolutionized the field of oncology, however, uncertainties remain regarding their best dosing regimen and individualization approaches with respect to adverse events and survival. For sunitinib, various strategies have been suggested, such as therapeutic drug monitoring (TDM) based on trough concentration measurements and toxicity-adjusted dosing (TAD) [1,2]. In addition, soluble biomarkers or, alternatively, neutrophil counts and blood pressure, have been related to overall survival (OS) in gastrointestinal stromal tumour (GIST) [2,3]. During the last years, TDM has gained momentum as a method to homogenize sunitinib exposure in clinical practice [4]. However, this approach does not account for the large inter-individual variability in the susceptibility of efficacy and safety endpoints [5]. Moreover, plasma concentration measurements for TDM may not be feasible in each country or treatment center due to practical and economical constraints. We explored an alternative, model-based, approach to increase OS in sunitinib-treated GIST patients, wherein dose-adjustments depend on pharmacodynamic biomarkers, such as adverse events (blood pressure and neutrophil counts), or soluble vascular endothelial growth factor receptor (sVEGFR)-3.

Methods: A previously developed pharmacodynamic framework describing the relations between sunitinib exposure, adverse events (hand-foot syndrome (HFS), fatigue, hypertension and neutrophil counts), sVEGFR-3 and OS [2,3] was further extended by a population pharmacokinetic (popPK) model [6]. The final framework of nine models was translated into mrgsolve [7] in order to evaluate dosing strategies by simulations. Intolerable toxicities were defined as ≥Grade 2 for HFS and thrombocytopenia and ≥Grade 3 for the remaining adverse events, as defined by the Common Terminology Criteria for Adverse Events v5.0 (CTCAE). Initial simulations were performed with fixed dosing regimens (4/2, 2/1 and continuous daily dosing [5]) and the best schedule, in terms of OS and adverse events, was selected as a base scenario. TDM, adverse event and sVEGFR-3-based dose adjustments were simulated according to an existing TDM schedule proposed by Lankheet et al. [4], with a discrete number of possible sunitinib doses (0 to 75 mg, by 12.5 mg increments). Finally, the accuracies of Bayesian maximum a-posteriori estimations were determined for various samplings schedules and the advantage of a model-based dosing algorithm for treatment optimization was explored.

Results: All models (including Markov and time-to-event models) were successfully implemented in mrgsolve. The continuous dosing schedule was found to give the best balance between AEs and OS, and therefore selected as a base scenario. AE-based dose adaptations increased median OS as compared to a fixed dose schedule (24.1 vs. 20.0 months; hazard ratio [HR] 0.90) and TDM-based dose adjustments (24.1 vs. 19.7 months; HR 0.81) without markedly raising the risk of intolerable toxicities. Similarly, sVEGFR-3-based dose adaptations increased median OS compared to fixed dosing (25.5 versus 21.7; HR 0.90) and TDM (25.5 versus 21.2 months; HR 0.77). Model-based predictions of blood pressure, sVEGFR-3 and neutrophils were accurate (80-125% of true value) for 28.5%, 64.6% and 73.5% of patients after three observations (routine sample at day 0, 15 and 29) and 35.1%, 76% and 85.6 % of patients after daily observations (day 0-29).

Conclusions: Biomarker changes were demonstrated to provide viable guidance for dose individualisation of sunitinib in GIST by increasing OS. AEs or sVEGFR-3 may therefore pose valuable alternatives to drug

concentrations (TDM). Neutrophil-based dose adaptations may however be preferred over sVEGFR-3, as neutrophils are readily measured in clinical practice and will not necessitate additional hospital visits or expenses. To our knowledge, this is the first framework-based Bayesian decision support tool for dose-individualisation that includes drug concentrations, soluble biomarker, adverse effects and OS. An external validation with clinical data could help to further confirm our proposal of biomarker-based dose adjustments.

Acknowledgement:
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References:
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[2] Hansson et al. CPT PSP (2013);2(12):e85. [3] Hansson et al. CPT PSP (2013);2(11):e84.
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B-08: *Chloe Pasin* Use of mathematical modeling for optimizing and adapting immunotherapy protocols in HIV-infected patients

Chloé Pasin (1,2,3), Laura Villain (1,2,3), François Dufour (4,5), Daniel Commenges (1,2,3), Mélanie Prague (1,2,3), Rodolphe Thiébaut (1,2,3)
(1) Univ. Bordeaux, INSERM, Bordeaux Population Health Center, France, (2) INRIA SISTM team, France, (3) Vaccine Research Institute, France, (4) Bordeaux INP, IMB, France, (5) INRIA CQFD team, France

Objectives:

In some cases, HIV-infected patients under antiretroviral therapy fail to restore their immune system and especially CD4+ T lymphocytes (CD4 in short) counts. Exogenous interleukin 7 (IL7) has shown beneficial effect to help increasing the number of CD4. A simple mechanistic model based on ordinary differential equations was developed to assess the effect of IL7 on CD4 proliferation, thymopoiesis and survival [1][2]. Then, phase I/II human clinical trials (INSPIRE studies) on 128 HIV-infected patients have shown that repeated cycles IL7 injections help maintaining HIV-infected patients with CD4 levels above 500 cells/µL [3], a level associated with a nearly healthy clinical status. Interestingly, the mechanistic model fitted very well the data although the distribution of the number of injections received was very different across the patients. Following this work, a question of interest was to determine optimal schedule of injections, to conduct the lightest intervention leading to the longest time above 500 cells/µL. We developed two approaches. One is based on the theory of optimal control and the other uses a Bayesian approach. Both methods succeeded in providing an optimal strategy for pseudo patients with different profiles, generated with the maximum a posteriori law obtained through previous parameters estimations on INSPIRE data.

Methods:

In the first method, we model the process with a Piecewise Deterministic Markov Process (PDMP), assuming that the patient's parameters are known and the stochasticity is due to the biological process. All actions realized on the process to modify its trajectory constitute a strategy, characterized by an optimality criterion balancing the time spent with CD4 levels below 500 cells/µL and the number of injections made. This criterion is minimized to determine the optimal strategy and its associated cost. Some theoretical results in [4] have shown that this minimization can be obtained through the iteration of an operator. This construction leads to a natural method of computation and enabled us to develop a numerical tool on Matlab. However, this method does not account for the uncertainty induced by the parameters estimation. The second approach deals with this issue by introducing random effects in a population model and estimating individual parameters with MCMC algorithm each time new information is available. Treatment can be adapted by using the predicted distribution of given criteria related to the CD4 trajectory. Two protocols are proposed: either the decision for a new cycle is based on the risk to fall below 500 cells/µL before the next visit, or the time of control visits are adapted.

Results:

We have used the optimal control method to determine the optimal cost and strategy for 50 pseudo patients on a horizon of one year. For all patients, the optimal strategy always gives a lower cost than other possible protocols and achieves a good balance between clinical criteria such as time spent with CD4 levels under 500 cells/µL, mean of CD4 cells/µL and number of injections realized. This strategy consists in first cycles of two injections until the number of CD4 is high enough and then one-injection cycles maintain the

CD4 levels over 500 cells/µL. In the Bayesian approach, the different protocols were simulated for 150 pseudo patients on a horizon of two years. All reduce the time spent under 500 CD4 cells/µL without increasing too much the number of visits and injections compared to the original protocol. Altogether these results confirm the possibility to adapt and optimize the strategy of IL7 injections.

Conclusions:

Both approaches can be used to adapt schedule of injections while maintaining patient above 500 CD4 cells/µL as long as possible. These positive results are also mainly attributed to the very good prediction ability of the deterministic model used for the dynamics of the CD4 cells. Although the optimal control method considers that the patient's parameters are known and induces large computing time, it could be more adapted if a deterministic model would not be sufficient to describe the biological process. The Bayesian approach is successful as it can be easily implemented on large horizons of time and accounts for the diversity of response of the patients without needing a long phase of learning. It offers clinical perspective, such as the evaluation of the adaptive strategy on clinical outcomes in larger trials.

References:

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B-09: *Mouna Akacha* Background on estimands and why are they important?

Mouna Akacha
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The topic of 'estimands' is shaking up the biostatistics community as it is at the heart of a draft addendum (ICH, 2017) to the ICH* E9 guideline (ICH, 1998) – the holy grail of pharmaceutical statistics. Broadly speaking, an estimand for a clinical trial represents "WHAT is most important to estimate in order to address the scientific question of interest" (Ruberg & Akacha, 2017).

The draft addendum presents a new framework which aims at facilitating a precise description of the treatment effect of interest by not only defining the population, the variable, and the population summary, but also by explicitly accounting for so-called "intercurrent events" which occur after randomization, e.g. treatment discontinuation due to an adverse event or the use of concomitant medications. Employing "estimand thinking" at the study design stage, whereby the team considers the impact of such intercurrent events on the WHAT will help in describing drug effects more precisely. The estimand framework may thus restore some of the intellectual health of clinical drug evaluation as primacy is re-assigned to "the questions we ask, not the methods by which we answer them" (Sheiner, 1991). Established practices in pharmaceutical research suggest that relatively more focus has been paid to the 'HOW' rather than to the 'WHAT'.

Furthermore, recent discussions on estimands have highlighted that some established paradigms in the pharmaceutical industry may not always be aligned with clinically meaningful treatment effect measures. One of these paradigms is the so-called intention-to-treat (ITT) approach – by some considered the "steadfast beacon in the foggy vistas of biomedical experimentation" (Efron, 1998).

The ITT approach came to prominence decades ago and was institutionalized in drug development with the publication of the ICH-E9 guideline in 1998 (ICH, 1998). The resulting analysis yields a treatment effect estimate that is often described as the effect of the treatment assigned at randomization or the treatment-policy effect. Despite its ubiquitous use in randomized, controlled clinical trials, the ITT analysis and its interpretation are neither consistently applied nor well understood by many. Indeed, the resulting estimates are sometimes difficult to interpret and may not provide an intuitive or clinically meaningful estimate of treatment effects (Sheiner(2002), Keene(2011)).

Alternative estimands to the treatment-policy estimand which are potentially more clinically meaningful are discussed in the draft addendum. However, deviations from the treatment-policy estimand implied through the ITT approach should not be taken lightly. For example, some estimands may be very relevant from a clinical perspective, but associated quantitative methods are complex and rely on various assumptions that cannot be verified from the data (Sheiner(2002), Nedelman et al. (2007)). In such cases, sensitivity analyses play an important role. Not surprisingly, the role of "sensitivity analyses" is also discussed in detail in the draft addendum.

More generally, the draft addendum is not about ITT or about statistics - rather it provides everyone involved in drug development with a language to have an early, more informed and transparent discussions with all key stakeholders (clinicians, regulators, payers, patients, etc.) to align on clinically meaningful trial objectives at the right time, i.e., during the protocol design phase (Akacha & Kothny, 2017). This is a very important opportunity for quantitative scientists who can guide the discussion, moderate it, and raise

important questions that will facilitate the choice of clinically meaningful estimands, targeted designs and appropriate analyses.

*ICH = International Conference on Harmonization

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B-10: *Michael Looby* PMX perspective on Estimands

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The concept of estimands in clinical drug development has re-emerged with the publication of the draft ICH E9 addendum. The concept is driven by efforts to address potential short-comings in intention to treat (ITT) analysis - only the randomized treatment assignment is taken into account in differentiating treatment groups at the outcome of a clinical trial. The new framework aims at facilitating a precise description of the treatment effect of interest by not only defining the population, the variable, and the population summary, but also explicitly accounting for events which occur after randomization, e.g. treatment discontinuation due to an adverse event, the use of concomitant medication, etc. The estimand discussion shifts the attention from the HOW to the WHAT in the design and analysis of confirmatory trials.

These questions of the *what* and the *how* in drug development occupied Lewis Sheiner in the early nineties, *Sheiner (1991)*. In particular, he drew attention to the properties and short-comings of ITT analyses and how these may be addressed using model based methods. *Sheiner and Rubin (1995)* introduced in this context the terms “use-effectiveness” – the causal effect of prescribing a drug, and “method-effectiveness” – the causal effect of actually taking a drug. The authors stated that ITT may provide a valid estimate of the former under specific circumstances, but never of the latter, which may be more important in drug development and ultimately clinical usage.

The terms use- and method-effectiveness were first used in the context of contraceptives. Use-effectiveness tells us about the typical effectiveness of treatments in real life: this helps policy makers to make recommendations on treatments. However, to assess the true clinical potential of a medicine or intervention, it is necessary to estimate method effectiveness. Achieving this goal is not trivial. It typically requires models and assumption rich analyses. In some cases, particularly in a confirmatory setting, it is impossible. Irrespective of the challenges in estimating method effectiveness, regulatory approval requires confirmatory trials to asses use effectiveness. While, the Draft E9 addendum focuses on achieving this goal even in the presence of significant inter-current events, I believe the focus on the clinically relevant questions at the study design stage is beginning to have benefits. For example, at a workshop in dose finding in 2014, the EMA stated: ”Traditional statistical pairwise comparisons in phase 2 trials to support dose selection by testing for statistically significant differences between the groups are not a regulatory requirement and are suboptimal in terms of dose selection”. “Mathematical, statistical and pharmacological methodologies to characterise D-E-R and optimal dose selection are scientifically well developed, available for application and welcomed by regulators. These should be tailored to the specific development needs”. As with many topics, this development of using the most appropriate analyses to address the key questions was anticipated by *Sheiner (1979)* with the learn and confirm paradigm.

In this talk, we will present two examples carried out prior to the publication of the E9 addendum. These examples demonstrate that PMX analyses, as anticipated by Sheiner, can play a central role on drug development and approval, especially when these analyses are closely coordinated with statistics.

The first example will show how a PMX analysis strategy can be used to learn about method-effectiveness efficiently across trails and ultimate lead to the confirmation and approval of novel regimens.

The second example demonstrates how a PMX analysis can be used to address method-effectiveness of a novel drug combination in transplant medicine and ultimately enabling regulatory approval that would have been unlikely otherwise.

The estimand framework is an attempt to restore "*the intellectual primacy to the questions we ask, not the methods which we answer them" Sheiner (1991)*. The discussion round the WHAT in clinical development is core to PMX and the discipline can be central to bringing focus to these questions together with our statistical colleagues. It is my firm belief that 'opening the box' on the '*what* questions' in drug development through the estimand framework will ultimately lead to wider use of model-based methodologies, because they are often the most effective or only way to address key questions such as method-effectiveness. It is also my belief that this transformation presages ever close integration of PMX and statistics.

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B-13: *Camille Vong* Power assessment for hierarchical combination endpoints using joint modelling of repeated time-to-event and time-to-event models versus Finkelstein-Schoenfeld method

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Objectives: Cardiovascular (CV) clinical trials often assess therapeutic benefit based on a survival event such as death. Additional reportable clinical outcomes preceding death, such as nonfatal myocardial infarction, hospitalization for heart failure, increase in blood pressure, etc. could be considered in combination with survival, while still preserving the hierarchy of their clinical importance in hypothesis testing, especially under a rare disease condition, when the number of patients is limited to investigate a treatment effect. Finkelstein-Schoenfeld (FS) [1] proposed a non-parametric test based on a score derived from 1) subject-to-subject comparison within the same stratum of their time to an event, and 2) if both subjects were censored, the comparison of the longitudinal measure of an ancillary endpoint. To differentiate doses, hence establishing a dose-/exposure-response relationship, the FS as a pairwise comparison method, requires multiple subgroup tests for which trials may be insufficiently powered. Additionally, FS ignores the assessment of the ancillary endpoint in patients who die in the trial, hence reducing the information about a possible correlation between the two endpoints. The objective of this work is to compare power performances to detect drug effect of joint PK/PD models of a mortality time-to event endpoint, combined with a repeated-time-to-event model (RTTE+TTE) of hospitalization frequency related to CV events and competing models for the purpose of informing a dose recommendation for a rare disease.

Methods: Simulated PK concentration, mortality and hospitalization data of a 30-month Phase 3 controlled trial with approximately 400 subjects enrolled in a 2:1:2 ratio (placebo:low:high), were generated from 100 stochastic simulations using the MTIME method in $DES [2] for three different drug effect scenarios: (a) similar for placebo and low dose, (b) similar for low and high dose, and (c) monotonic Emax relationship between placebo, low and high doses.

Simulated data were analysed in NONMEM 7.3 [3] with the following structural models: a time-to-event (TTE) model, a repeated time-to-event (RTTE) model, a time-to-event model with hospitalization frequency as a time-varying covariate (TTE-COV), and two RTTE+TTE models linked (a) by an individual exposure (RTTE+TTE 1), (b) by a common hazard with a scaling factor between the 2 mechanisms (RTTE+TTE 2). Model evaluation was carried out through simulation-based Kaplan Meier representations, binned and kernel hazard VPCs [4], and aiming for model stability. Power versus sample size curves for each model were calculated using the parametric power estimation (PPE) algorithm [5]. FS analytics were generated in SAS 9.4 [6] as the reference power for each scenario.

Results: For all 3 scenarios investigated, the median estimated PPE curves were in general in the following order: TTE, FS, TTE-COV, RTTE or RTTE+TTE 1, RTTE+TTE 2. For instance, the power to detect drug effect at the original simulated sample size, was 30%, 44%, 54%, 55%, 59%, and 72%, respectively for scenario (c). The convergence rate for RTTE+TTE 1 and 2 were 78 and 91%, respectively. In scenarios (a) and (b), EC50 was estimated with mean precision of 16.4% and 156.5%, respectively. Type I error rates for the respective models were found to be 1%, 4%, 6%, 7% and 5%, respectively.

Conclusions: Using both survival and hospitalization data in patients who died or were otherwise censored suggests that the power to detect a drug effect can be substantially increased using the proposed joint PK/PD models. RTTE+TTE-type models demonstrate multiple benefits, such as a higher power by enabling a two-dimensional evaluation of an exposure-response relationship and also by utilizing all available information for each patient. Thus, they may be considered for smaller sample sizes to detect the same treatment effect in future trials.

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B-14: *Yixuan Zou* A novel score test-based method for efficient covariate selection in population pharmacokinetic analysis

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Objectives:

Originally proposed Wald's approximation method (WAM) [1], least absolute shrinkage and selection operator (LASSO) [2] and stepwise covariate method (SCM) [3] are three common covariate model selection approaches in population pharmacokinetic (PPK) analysis. However, covariance matrix of the full PPK covariate model for WAM calculation is very sensitive to study design/model selection and can be difficult to obtain in PPK analysis. LASSO has poor performance in PPK analysis with large datasets and also requires running the full PPK covariate model with constraints on all parameters. The number of NONMEM runs for SCM can be prohibitively large with increasing number of tested covariates and model parameters. Therefore, the objective of this study was to develop an innovative and efficient covariate screening method using score test with the base PPK model without covariates to overcome the drawbacks of WAM, LASSO and SCM in PPK.

Methods:

First, the score test-based method used second order finite difference to calculate the score function and observed fisher information matrix (FIM) at the covariate parameter value of zero in the base PPK model without any covariates. No actual model run was needed to obtain the score function and observed FIM. The obtained score function and observed FIM were then used to determine the score statistic for covariate model selection. Two different model/study design scenarios each with 20 simulated datasets were used. The first scenario was a one-compartment linear PK model with intensive sampling design (number of simulated subjects or N=50, 100, and 200). Among the six covariates used in this scenario, the model parameters clearance (CL) and volume (V) were only affected by weight and gender. The second scenario was an original PK sampling design of a phase II clinical study used to develop the two-compartment PPK model of rituximab [4] (N=107). Thirteen covariates were evaluated in this scenario and both CL and central volume (Vc) were affected by body surface area and gender. Two different score test-based methods were developed and compared to SCM. In the first approach (score test coupled with SCM, or SSCM), forward selection (FS) based on score statistic was used to efficiently yield the preliminary covariate model that was subject to SCM with actual NONMEM runs for final covariate model selection. The second approach (score test coupled with backward elimination, or SBE) used the same score statistic-based FS but was followed by backward elimination (BE) with actual NONMEM runs for final covariate model selection. Relatively less stringent model selection criteria (p=0.2) was used in FS of the score-test covariate screening process as the score statistic has been shown to be more conservative than the likelihood ratio test in linear models [5]. SBE used a significance level of 0.01 in BE after the score test screening. SSCM used a significance level 0.05 in FS and 0.01 in BE after the score test screening. SCM used the same significance levels in FS and BE as SSCM.

Number of correct (true positive) and incorrect (false positive) covariates included for the three methods were used to assess the accuracy of the method in covariate selection. In addition, the average numbers of actual NONMEM runs were also recorded and compared. R (version 3.4.3) and Python (version 2.7.14) were used for covariates simulation and automated NONMEM (version 7.30) runs, respectively.

Results:

For the first scenario, SSCM and SBE achieved comparable accuracy with significant fewer actual NONMEM runs compared to SCM. The following table shows the average actual NONMEM runs for final model covariate selection for different methods:

Number of simulated subjects	SBE	SSCM	SCM
50	17	25	49
100	9	17	46
200	13	20	48

For the second scenario, the SCM identified more true positive and fewer false positive covariates compared to SSCM and SBE but at the expense of more actual NONMEM runs (39[SBE]<58[SSCM] <132[SCM]).

Conclusions:

In this study, two innovative score test-based covariate model development methods (SSCM and SBE) were developed. Both of these models needed fewer actual NONMEM runs compared to SCM and were very useful for covariate model development in presence of large number of covariates and long computation time of a single NOMEM run in complex quantitative system pharmacology analysis.

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B-15: *Qing Xi Ooi* Evaluation of assumptions underpinning pharmacometric models

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Background: All models are underpinned by assumptions. The validity of any inference drawn from a model depends on the appropriateness and likely impact of the underlying assumptions [1]. Assumption evaluation is therefore an integral part of model building and model use. Current guidelines by the Food and Drug Administration (FDA) [2], the European Medicines Agency (EMA) [3], and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [1] stipulate that all assumptions inherent to model development and model application should be explicitly expressed and evaluated. However, in the literature surrounding pharmacometric models, assumptions are not routinely acknowledged, described, or evaluated. This is also apparent in the analyses submitted for regulatory review, where the EMA outlined the lack of transparent description of influential assumptions and an ineffective evaluation or reporting of the impact of assumptions on model inference to be a major limitation [4]. These form an important barrier for effective model use and regulatory review. Here, while the importance of assumption evaluation is well-recognised, how these assumptions should be systematically approached and be effectively assessed has received limited attention.

Objectives: In this work, we proposed a framework for evaluating assumptions systematically that is generalisable to both top-down and bottom-up pharmacometric model development. The objectives of this work were:

1. to define an assumption within the context of this work,
2. to develop a flowchart for systematic evaluation of assumptions,
3. to propose a standardised table for documentation of assumptions and evaluation results, and
4. to apply the flowchart to a top-down and a bottom-up model.

Methods: Medline (1946 – December 2017), EMBASE (1947 – December 2017), Google Scholar (1947 – December 2017), as well as the websites of medicines regulatory authorities were searched for pharmacokinetic and pharmacodynamic guidelines and good practice papers. Subsequently, these papers were screened for methods related to evaluating model assumptions. Relevant papers were mined for additional articles. Two key articles by EFPIA [1] and Karlsson et al. [5] provided specific frameworks for evaluating model assumptions and were used as a starting point for this work. The existing frameworks were expanded based on an evaluation of the risk management literature, expert opinion, and logical reasoning. The typical workflow for assumption evaluation was generalised into a qualitative flowchart. The flowchart was developed in a stepwise manner. In the first step, a decision tree that mapped all possible outcomes from a sequential evaluation of the impact and the probability of assumption violation was built. In the next step, the multilevel decision tree was streamlined to a simple flowchart for assumption evaluation. Subsequently, a table was designed based for documentation of assumptions and evaluation results. The utility of the flowchart was illustrated for both: (a) a top-down model building process and (b) a bottom-up work based on a quantitative systems model. The top-down approach was based on a kinetic-pharmacodynamic (KPD) model for warfarin and the coagulation proteins [6]. For the bottom up approach, we considered the development of a warfarin dosing method based on a systems coagulation network model [7].

Results: For the purpose of this work, an assumption is defined as a perception of the truth that can be distinguished from a hypothesis (a testable belief), an axiom (a self-evident belief), a theorem (a proven belief) and a limitation (a boundary beyond which the assumption no longer holds). We categorise assumptions into two types: (a) implicit in which a theorem is being relied upon to form a framework of the modelling process (e.g. linearity between two variables if relationships were to be quantified using Pearson correlation); (b) explicit which arises from a gap in knowledge for which an imputation by the investigator will be required (e.g. heuristic application of a Michaelis-Menten model to describe a system response for which we have no prior knowledge). To be exhaustive in identifying assumptions, modellers are encouraged to list the assumptions systematically according to the nature of the assumption: (a) biological or physiological, (b) pathophysiological, (c) pharmacological or pharmaceutical, (d) experimental, (e) study conduct, and (f) statistical or mathematical assumptions.

A flowchart for the systematic evaluation of assumptions was developed. For each assumption, the impact of assumption violation, *I* ("significant", "insignificant", "unknown"), is first assessed to stratify risk. If *I* is significant or unknown then the probability of assumption violation, *P* ("likely", "unlikely", "unknown") is evaluated. Here, the ratings for *I* and *P* are rated based on prior knowledge or the result of an additional bespoke study (often a simulation study), termed posterior. In this work, both *I* and *P* are evaluated for their influence on: (a) an internal component of the model building, or (b) an external use of the model (i.e. a circumstance in which the model is used for inference other than for the data that was used to build the model). The outcomes of the flowchart included go / no-go decision for internal and external use of the model. The decisions may be accompanied by an acknowledgement of the assumption as a limitation, for instance, when *I* is unknown but *P* is unlikely in the specific current scenario. For documentation of assumptions and evaluation results, an assumption table with standardised headings ("assumption", "prior or posterior *I* or *P* (subheadings: 'evaluation methods', 'results', 'ratings')", "action point", "decision") are proposed.

Finally, the utility of the flowchart was demonstrated using assumptions from both top-down and bottom-up model. For brevity, only one assumption from each type of model is illustrated here. Using the KPD model example, *I* was found significant and *P* unlikely for the assumption "residual errors are normally distributed" thereby giving a final go decision for model building. For the systems model example, the assumption that "the model developed accurately describes factor VII and the anticoagulant response" was associated with significant *I* and likely *P* owing to the biased predictions produced beyond the dose range modelled. This resulted in a no-go decision for external model use.

Conclusions: A framework for systematic evaluation of assumptions is proposed and its utility is demonstrated using both top-down and bottom-up examples. The next step of this work is to apply the framework to a series of other settings to fully assess its practicality and its value in identifying and making inference from assumptions.

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B-16: *Mats Karlsson* Extensive and automatic assumption assessment of pharmacometric models

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Objectives: The reliable use of Nonlinear Mixed Effects Models (NLMEM) in decision-making is based on the appropriateness of the assumptions underpinning the model (1-3). Therefore, we develop methodology that involves (i) comprehensive and exhaustive assessment of the probability of assumption violations, (ii) metrics for the expected impact of any assumption violation, and (iii) specific advice on action(s) likely to avoid or rectify a particular assumption violation. In particular, we develop for this purpose "model-proxy analyses", i.e. analyses that provide the same information as testing a new model (change in goodness-of-fit/OFV, parameters, predictions, etc.) but in a robust and time-efficient manner.

Methods: The scope of assumption assessments we consider includes most aspects testable on data and include six sections: (i) structural, (ii) covariate, (iii) parameter and (iv) residual model components as well as (v) influential individual and (vi) outlier assessments. For this purpose recent (4,5) and new (6-9) methodology based on analyzes of linear(ized) mixed effects models (LMEM) has been compiled and integrated. The methodology is implemented as the "QA" package in the PsN software. Basic arguments to the assessment are the model to be evaluated together with the parameters and covariates of interest. Both covariates already included in the model as well as those not included can be elements of the investigation. The output of the QA routine is a structured pdf-report providing top-level information about what aspects of the model which may or may not be associated with assumption violations and directions to further in-depth results. The performance of the QA routine was evaluated on 30 previously published models available in-house, from collaborators or retrieved from the DDMoRe model repository.

Results:

Average characteristics of the 30 models were: 139 subjects (range 8-644), 3.9 parameters (1-8) and 3.8 covariates (1-10) resulting in an average of 207 (54-700) proxy models that on average completed execution in a total of 12 (2-90) min. While limitations in scope and other shortcomings (i.e. bugs) resulted in some failed runs, the overall success rate was at least 90% for all 6 sections and 100% for the structural, parameter variability and residual model sections.

The structural model section assesses the assumption of lack of bias in predictions. This is evaluated with respect to independent variables such as time and prediction. The output is presented as (i) potential improvement in goodness-of-fit (OFV) to be gained by avoiding structural model bias, (ii) the magnitude of bias (back-calculated from CWRES using the FOCE approximation), and (iii) a graphical (VPC) representation of the original and bias-corrected model.

The parameter variability section assesses extensions exploring full covariance matrix models, allows skewed or heavy-tailed distributions for the random effects and the need for additional interindividual or interoccasion random effects. For each component the improvement in OFV, the change in parameter values and in parameter distribution shape is provided.

The residual variability section provide extensions with respect to serial correlation, distribution skewness, t-distributed errors, time-varying or interindividual error magnitudes and presents improvement in OFV, change in parameter estimates and expected change in precision in structural parameter estimates.

The covariate section present both univariate (SCM) and full model assessments of covariates providing improvement in OFV, magnitude of improvement, Forest plots, variability explained and extreme individual information.

The influential individual section focuses on individuals for which the omission importantly change the description of the model for the remaining individuals.

The outlier analysis differentiates between outliers due to individual observations and due to outlying parameter value, where possible.

Conclusions: A comprehensive evaluation of assumptions that are to be assessed based on data has been presented, implemented and evaluated. Advantages over graphical assessment of a final model is that it is objective, specific on what assumption is violated and predictive of the consequence of a model change. Compared to running new models it is fast, robust and automated. It is easy to use and while of particular value at the final stages of model development, it may improve modelling at any stage of refinement.

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B-18: *Oskar Alskär* An integrated glucose homeostasis model of glucose, insulin, C-peptide, GLP-1, GIP and glucagon in healthy subjects and patients with Type 2 diabetes

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Background

The glucose homeostasis is complex and involves several hormones and regulatory systems. Currently available models such as the integrated glucose insulin (IGI) model is capable of describing glucose and insulin during intravenous glucose tolerance tests (IVGTT), oral glucose tolerance tests (OGTT) and meal tolerance tests[1-4]. However, these models have empirical elements, such as the description of glucose absorption and the incretin effect that limits their extrapolation properties. In addition, the models do not provide a description of other important hormones such as glucagon.

Objectives

To develop a mechanism-based pharmacometric model that can describe concentration of glucose, gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), C-peptide, insulin and glucagon during glucose tolerance tests in healthy individuals and patients with type 2 diabetes (T2D).

Methods

The data used in this analysis originates from a study by Bagger et al [5,6]. The study included eight patients with T2D and eight sex- BMI- and age-matched healthy individuals. The participants were studied at six different occasions; first three OGTTs with the doses 25, 75, and 125 g of glucose were performed. The rate of gastric emptying was monitored by inclusion of 1.5 g of acetaminophen in the oral glucose solutions. On the following occasions, three isoglycaemic intravenous glucose infusions were performed that mimicked the glucose profiles from each of the OGTTs. Blood was frequently sampled during 4 hours (10 samples of glucagon, GIP, GLP-1 and acetaminophen, 15 samples of C-peptide and insulin and 20 samples of glucose). To obtain more information on insulin secretion, insulin data from four previously published IVGTT studies were also included in the analysis[7-10]. Three studies included healthy individuals (totaling 64 individuals) and one included patients with T2D (42 individuals). A bolus glucose dose of 0.25-0.33 g/kg was given and blood frequently sampled up to 180-240 minutes, for determination of glucose and insulin concentrations. In one study of healthy individuals and the study of patients with T2D insulin was infused over five minutes, 20 minutes after the glucose dose.

Model development was divided into four parts, each describing a subset of the data. 1) Paracetamol and glucose, 2) GLP-1 and GIP, 3) C-peptide and insulin, 4) Glucagon and endogenous glucose production. During development of each submodel the observed concentrations of the different biomarkers were used as time varying covariates to reduce runtime and complexity of the model. For GIP, GLP-1 and glucagon half-life were set to literature values. Non-Linear Mixed Effect Models (NONMEM version 7.3) [11] with the first order conditional estimation (FOCE) method and the differential equation solver ADVAN13 was used

for the population data analysis. A stringent significance level of 0.1 or 1% was used to avoid over parametrization.

Results

Four submodels were developed describing:

1) Gastric emptying and glucose absorption[12]. After a 5-minute lagtime gastric emptying started and the inhibition of gastric emptying was described by a negative feedback of duodenal glucose. To be able to describe glucose movement through the small intestine it was assumed that the total transit time was 240 minutes and that the duodenum, jejunum and ileum comprised 8%, 37% and 55% of the total length respectively[13]. Saturable absorption of glucose from each intestinal segment was included.

2) Regulation of GIP and GLP-1 secretion[14]. GIP and GLP-1 was described by turnover models with the elimination rate constant fixed, corresponding to literature values. Secretion of GIP was stimulated by duodenal glucose while GLP-1 was stimulated by jejunal glucose.

3) Incretin effect and hepatic extraction of insulin. Secretion of insulin and C-peptide from beta-cells was described by adapting the mathematical beta cell model developed for healthy individuals by Overgaard et al.[10]. Two structural modifications were made to be able to describe the data for patients with T2D. 1) The first-phase secretion of insulin/C-peptide from the passive to the active vesicles was excluded from the model. 2) The fraction of active vesicles was found to be independent of glucose, and thus fixed to the fasting condition. By coupling the shared secretion model with disposition models for C-peptide and insulin it was possible to characterize the hepatic extraction of insulin. The insulinotropic effect of the incretin hormones GIP and GLP-1 was also characterized. Both GIP and GLP-1 were shown to stimulate provision of new insulin/C-peptide and activation of vesicles for healthy individuals. Patients with T2D were assumed to have no effect of GIP in accordance with literature[15] and GLP-1 was shown to mainly affect the activation of vesicles.

4) Regulation of glucagon secretion and endogenous glucose production. During both OGTT and IIGI, glucagon concentrations decrease quickly and stayed suppressed under the baseline throughout the study, even though insulin and glucose returned to baseline. A model where glucose potentiates the inhibitory effect of glucose and insulin on glucagon synthesis over time through a series of transit compartments was estimated to capture the prolonged suppression. This model allows for initial rapid suppression when glucose and insulin concentrations are high, as well as sustained inhibition after the concentrations have returned to baseline. Patients with T2D were shown to have stronger net stimulatory effect of the incretin hormones compared to healthy individuals, explaining the initial hypersecretion of glucagon seen in patients with T2D. The combined effect of glucose, insulin and glucagon on endogenous glucose production was also determined.

All submodels were combined into one comprehensive mechanism-based model capable of simultaneously describing the most important aspects of glucose homeostasis during glucose tolerance tests in healthy individuals and patients with type 2 diabetes, over a wide range of oral and intravenous glucose doses. The approach of developing each submodel conditioned on biomarker observations and then combining the submodels was here show-cased to work well and reduced the complexity of model development considerably.

Conclusion

In conclusion, four submodels each describing different aspects of glucose regulation were successfully combined into a new comprehensive mechanism-based model describing glucose homeostasis. The developed model is covering the most important hormones and mechanisms of glucose homeostasis and

may be used to investigate combination treatments, drugs with multiple effects and to improve drug development of new antidiabetic compounds.

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B-19: *Daniel Hill-McManus* Application of a linked pharmacometric/pharmacoeconomic model to assess the impact of non-adherence: Application to the treatment of gout

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Introduction

A natural extension to pharmacometric analyses, exploiting the structural relationship between dose and response, is to link with pharmacoeconomic models which consider the resource constraints of payers of healthcare [1, 2]. One potential application is to estimate the impact of imperfect adherence patterns on modelled economic outcomes.

Medication adherence can be decomposed into three distinct phases; 1) initiation, 2) the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation) and 3) and persistence [3]. An important limitation of conventional economic modelling is its limited capacity to account for the impact of poor implementation, which may lead to biased estimates of treatment effect and confound the results of cost effectiveness analyses [4].

Dual urate-lowering therapy (ULT) with lesinurad in combination with either allopurinol or febuxostat is an option for gout patients unsuccessfully treated on either monotherapy. Medication adherence is known to be especially poor for ULTs [5] and may often result in treatment failure [6].

Objectives

The aim of the present study was to predict the impact of variable adherence, using PKPD simulations, on the cost-effectiveness of treatments for gout.

Methods

Compartmental pharmacokinetic models for allopurinol, febuxostat and lesinurad were obtained from the literature [7–9] and used to simulate drug plasma concentration time courses with varying implementation patterns in a hypothetical patient cohort. Three adherence scenarios were used in simulations, the first being the hypothetical best-case scenario of perfect adherence. The second and third used treatment persistence based on discontinuation observed in lesinurad pivotal trials [10, 11], and average levels of dose implementation of 50 and 80% respectively.

The time course of serum uric acid (sUA) was simulated using a semi-mechanistic, 4-compartment pharmacodynamic model which captured both the inhibition of sUA formation via the inhibition of xanthine oxidase (action of allopurinol and febuxostat) and its increased clearance via inhibition of URAT1 (action of lesinurad) [12]. Parameters were either extracted from previous PKPD studies and trial reports or were estimated using nonlinear mixed effects modelling in NONMEM 7 [13]. A bespoke pharmacoeconomic model was developed, with reference to previous economic evaluations of ULTs [14, 15]. The linked PKPD and pharmacoeconomic model was used to estimate the costs and quality-adjusted life-years (QALYs) accrued over patients' lifetimes for different treatment and adherence scenarios.

Results

Providing lesinurad dual therapy to non-responders on allopurinol monotherapy is estimated to result in an additional 0.067 QALYs at an additional cost of £3,470 per patient. The resulting incremental cost effectiveness ratio (ICER) is therefore £51,622 per QALY. The estimated ICERs increased with worsening adherence, to £55,665 and £92,064 per QALY in scenarios including discontinuation and implementation rates of 80 and 50% respectively. The equivalent ICERs using febuxostat as monotherapy ranged from £42,052 to £147,934 per QALY.

The quarterly price of lesinurad resulting in an ICER of £20,000 per QALY (value-based price), assuming perfect medication adherence, was estimated to be £34.35 when used in dual ULT compared with allopurinol alone and £43.25 compared with febuxostat alone. This fell to £22.59 and <£0 respectively in simulations of worsening medication adherence. These quarterly prices fall below the list price of £85 per quarter quoted during its recent appraisal for reimbursement in the United Kingdom [16].

Conclusion

Linked PKPD and pharmacoeconomic modelling provide a means of studying the implications of drug pharmacology and adherence on the economic potential of new medicines [17]. Medication adherence has a significant influence on the potential cost effectiveness of second-line dual-ULT with lesinurad compared with either allopurinol or febuxostat alone. The highest value-based price of lesinurad found assuming perfect drug adherence was still below that which has been proposed for the UK market [16]. For health care payers, prescribers and patients these results provide an indication of the extent to which poor adherence to ULTs erodes the cost effectiveness of these medicines when translating from clinical trials to routine practice.

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C-01: *Simon Buatois* A pharmacometric extension of MCP-MOD in dose finding studies

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Objectives:

Finding the right dose remains a crucial milestone in clinical drug development [1]. According to the ICH-E4 guidance [2]: "dose finding should rely on model-based estimation rather than hypothesis testing via pairwise comparisons". In this context, the multiple comparison procedures and modeling (MCP-MOD) technique [3,4] received an EMA and FDA qualification opinion as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. Starting from a predefined set of candidate models, MCP-MOD is a two steps approach which, first, establishes the evidence of a drug effect using multiple contrast tests (MCP step) and, then estimates the dose to be brought into the confirmatory phase using a model based approach (MOD step).
In its current implementation, however, the MCP step is limited to the exploration of several mean dose response functions measured at end of trial and, hence, ignores longitudinal information. The consequence is a reduction in power. Pharmacometric analyses (PMX), on the other hand, utilize all the data but generally involve the process of model selection which ignores model structure uncertainty [5–7] and may lead to type I error inflation.
The objective of this work was, therefore, to extend the MCP-MOD methodology and allow for longitudinal nonlinear mixed effects models (NLMEM) for both MCP and MOD step. An additional objective is to evaluate the merits of model selection (MS) and model averaging (MA) for the MOD step through clinical trial simulations (CTS) under various designs and various dose effect models.

Methods:

MCP-MOD extension:
The proposed extension utilizes a predefined set of NLMEM for both MCP and MOD steps. This set is referred to as candidate models.
In the MCP step, the presence of a drug effect is tested using a likelihood ratio test (LRT) between the reference model (i.e.: no dose response relationship) and the best candidate model (MS) according to the Akaike information criterion (AIC) obtained after fitting each model to the data. The critical value for the test is derived through 500 simulations of the same selection procedure under the null-hypothesis with parameter values obtained from the placebo arm of the study (corrected LRT).
In the MOD step, either the candidate model that best describe the data is selected (MS) or a weighted mixture of the candidate models is used (MA).

Evaluation:
CTS were used to evaluate the proposed extension in terms of the following metrics:
- Maintenance of the nominal (5%) type I error in the MCP part per se and in comparison to a non-corrected LRT. For the latter, the distribution of the changes in objective function is summarized for each candidate model and followed by a classical MS. Type one error rate was assumed to be adequate if it was within the 2.5^{th} (3.2%) and 97.5^{th} (7%) percentiles of a binomial distribution with a probability of success of

5% on 500 trial replicates.
- Coverage probability in the MOD step, defined as percentage of trial where the 95% confidence interval contained the true value of interest which could either be a percentiles of the response distribution between the placebo and treatment arms at end-of-treatment, or the minimum effective dose. Coverage was assumed to be adequate if it was within the 2.5^{th} (93%) and 97.5^{th} (96.8%) percentiles of a binomial distribution with a probability of success of 95% on 500 trial replicates.
The evaluation was performed under various simulation scenarios of a hypothetical phase II clinical trial for a monoclonal antibody indicated in the treatment of wet age related macular degeneration (wet-AMD). The duration of the study was set to 12 months with 5 parallel arms (placebo or one of following doses 100, 200, 400 and 1000). Observation times are at baseline, day 7 & every month during 12 months. Finally, two sample size were investigated assuming either 300 (60 per arm) or 50 (10 per arm) patients. Clinical trial simulations were based on a simplified version of a disease model which characterizes the time course of visual acuity (VA) of wet-AMD patients [8] plus one of 5 symptomatic drug effects (no drug-effect, Linear, Log-linear, Emax, and Sigmoid-emax). The resulting 10 scenarios were simulated 500 times.

Implementation:
All simulation and estimation were performed using NONMEM 7.4 with importance sampling estimation algorithm. For each simulated dataset and each candidate model 1000 population parameters were drawn from a multivariate normal distribution where the mean were set to the maximum likelihood estimates and the variance to the variance covariance matrix of the estimates. Using MS, the population parameters were drawn from the best candidate model and using MA, a probability was associated to each one of the candidate models [9]. Finally, 50000 Monte Carlo simulations were used to compute the different values of interest.

Results:

Regarding the MCP part, the type I error rate of the corrected LRT was adequate and equal to 6.2% and 4.6% for the design with 300 and 50 patients, respectively. Using an uncorrected LRT, a substantial increase of the type I error rate was found for both sample size (up to 9.2%).
Regarding the MOD part, the design with 300 patients was associated to adequate coverages for MA and MS. Under the Log-linear and Emax simulation scenarios, the MA method was tending to over-estimate model uncertainty (coverage up to 98.8%) when the MS method was under-estimating the confidence intervals (coverage down to 91.2%). Under the design with 50 patients, MA was leading to better coverage performances than the MS. Coverage performances were mostly adequate under the Linear and Log-linear scenarios and below the lower boundary for the remaining simulation scenarios.

Conclusions:

This work extends the MCP-MOD methodology to use NLMEM in both MCP and MOD step. By deriving the reference distribution of the LRT under the null-hypothesis the method maintains the nominal type-I error while using the full longitudinal information. The work, furthermore, shows how model averaging provides substantially better coverage in the MOD step, and how the ignorance of model uncertainty leads to an under-estimation of the confidence intervals.

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C-02: *Benjamin Guiastrennec* New dosing recommendations for anti-tuberculosis therapy in Indian children

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Objectives: Pediatric dosing recommendations of first line anti-tuberculosis (TB) treatment are based on pharmacokinetic (PK) studies in adults.[1] Yet new evidence revealed that small children are often underexposed and could lead to poor clinical outcomes.[2] India has the highest TB burden in the world, accounting for 27% of total incident cases.[3] In November 2017, India officially switched from a thrice-weekly to a daily dosing, although still relying on a constant mg/kg dosing across the different pediatric weight bands.

The present work aimed 1) to characterize the PK of the first line anti-TB drugs isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA) in underweight Indian children undergoing thrice weekly dosing as per previous Indian pediatric dosing recommendations, 2) to establish the relationship between the plasma exposures of these drugs and the anti-TB treatment outcome, 3) to evaluate the previous and new Indian pediatric dosing recommendations and finally 4) to propose optimized dosing recommendations via a model-based approach.

Methods: The clinical data were pooled from two studies in 161 Indian children (1–15 yr, 6–44 kg) diagnosed with drug sensitive TB [2], 84 of whom had human immunodeficiency virus (HIV) coinfection [4] and also received anti-retroviral therapy. After at least two weeks of thrice-weekly anti-TB treatment, the plasma concentrations of INH, RIF and PZA were measured at 0, 2, 4, 6 and 8 h following dose intake.

Published population PK models in South-African children featuring maturation functions and delayed absorption, were used as starting point.[5] All clearances and volumes were allometrically scaled to the total body weight using exponents of ¾ and 1 respectively.[6] Non-linearity in absorption and elimination were evaluated using a Michaelis-Menten type parametrization. A stepwise covariate modeling (SCM) approach with forward inclusion ($p<0.05$) and backward deletion ($p\geq0.01$) steps was used to explore additional effects of total body weight, nutritional status (z-scores) and HIV-related covariates on the clearance, volumes, relative bioavailability and absorption delay.

The treatment outcome at 6 months – reported as favorable (cure/treatment completion) or unfavorable (death/treatment failure) – was modeled using a logistic regression model. The covariates and individual model-predicted weekly exposures (i.e. area under the concentration time curve) of each drug were evaluated as predictors of the treatment outcome through a second SCM.

The selected PK-PD model was used to evaluate through simulations (n = 1000) the probability of unfavorable treatment outcome ($P_{unfavorable}$) under the previous thrice-weekly and new daily pediatric Indian dosing recommendations. Optimized doses were proposed based on a $P_{unfavorable}$ of 5% or less.

Parameter estimation was conducted in NONMEM v.7.3, using the FOCE-I estimation method for continuous data and the Laplacian method for categorical data.

Results: In total, 805 plasma concentrations were collected for INH, 794 for RIF, and 720 for PZA. Samples below the detection limit (INH: 148, RIF: 174, PZA: 75) were mostly represented by trough concentrations and were excluded from the analysis.

Drug distribution was biphasic for INH and monophasic for RIF and PZA. The PK of all three drugs was linear over the studied doses ranges and all also displayed significant delays in absorption (i.e. ≥0.98 h). The estimation of the absorption rate constants was supported by the use of frequentist priors. The estimated clearances for INH and RIF were significantly lower (-24% and -46% respectively) than reported values for similar studies in South-African children, while PZA clearance was similar in both populations.[5] For all three drugs, the predictions were significantly improved when the relative bioavailability was scaled to total body weight through a power relationship, indicating lower exposure in smaller children. In addition, HIV coinfection influenced the relative bioavailability of INH (-20%) and RIF (-42%) as well as the clearance of RIF (+32%). Finally, the fast INH metabolizer status was associated with a decreased relative bioavailability (-21%) and an increased clearance (+94%) compared to the normal metabolizers. For all three drugs, the between subject variability (BSV) in clearances and volumes was substantial (>34% coefficient of variation (CV)) and for RIF, BSV was also increased with HIV coinfection (clearance: +74%, volume: +106%) as compared to subjects with TB monoinfection.

The treatment outcome was favorable in 109 children (68%), unfavorable in 33 (20%) and unknown in 19 (12%); the latter were excluded from the PD analysis. Weekly RIF exposure (range, 9.81–231 µg.h/mL) was the only statistically significant independent predictor of treatment outcome. No statistically significant effect of INH (p=0.74) or PZA (p=0.81) exposures could be detected on $P_{unfavorable}$ within the observed exposure ranges (INH: 3.89– 346 µg.h/mL and PZA: 351–2780 µg.h/mL).

Under the previous thrice-weekly dosing regimen, the highest incidence of poor treatment outcome (mean $P_{unfavorable}$ up to 35%) was linked to low RIF exposure in HIV coinfected and small (<10 kg) children. Overall, the situation has improved under the new Indian daily dosing regimen, however the mean $P_{unfavorable}$ remained high in small and especially in HIV coinfected children (mean $P_{unfavorable}$ up to 25%).

The weekly RIF target exposure (i.e. $P_{unfavorable}$≤5%) was defined to 185 µg.h/mL. Optimized daily RIF pediatric doses were computed using this target exposure and given different weight bands and HIV coinfection status. In comparison to the Indian guidelines, the predicted optimized doses were mostly increased for children with low body weight (<10 kg) and especially for children with TB-HIV coinfection, with doses up to 43.4 mg/kg. For heavier children (>25 kg), the model predicted that the target exposure could be achieved with daily doses as low as 5.2 mg/kg.

Conclusions: The previous thrice-weekly and new once daily Indian pediatric dosing recommendations were evaluated through a population PK-PD approach linking the anti-TB exposure to $P_{unfavorable}$. Under the previous thrice weekly dosing regimen, an increased risk of poor treatment outcome was seen in children with low total body weight and with TB-HIV coinfection. Under the new once-daily dosing regimen the predicted treatment outcome showed an overall improvement, although children with low body weight (<10 kg) and TB-HIV coinfection are still expected to display high rates of poor outcome due to the use of constant mg/kg doses across the different weight bands. Optimized RIF doses were computed based on a weekly target exposure. The clinical practice in India is evolving and this work has the potential to support the design of new clinical trials exploring the safety and efficacy of higher RIF pediatric doses as it is currently the case in adults.[7]

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C-03: *Jurgen Langenhorst* Cause-specific hazard models with markovian elements to quantify the fludarabine exposure-response relationship: from learning to confirming in allogeneic hematopoietic cell transplantation

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Objectives:

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for a variety of malignant and benign hematological disorders. Unfortunately, non-relapse mortality (NRM, 10-40%) and disease relapse (20-50%) remain major causes of therapy failure[1], thus further treatment optimization is potentially life-saving.

The conditioning regimen prior to HCT consists of a combination of cytotoxic agents (chemo- and serotherapy) administered to eradicate recipient's bone marrow and immune system. Reducing the toxicity while maintaining the efficacy of such regimens is one of the key strategies to reduce NRM.[2] Fludarabine combined with busulfan and anti-thymocyte globulin is a commonly used conditioning regimen for HCT and a profound influence of all these agents[3-5] on HCT outcomes has been established.

However, the relationship between fludarabine exposure and HCT's main outcomes event-free survival (EFS: absence of NRM, relapse, and graft failure) and overall survival (OS) is complex. There is an increased probability of graft failure at low fludarabine exposures,[6] an inverse relationship with NRM,[7, 8] and no relationship with relapse.[5] In addition, NRM and OS are directly connected, but graft failure and relapse are not necessarily followed by death.

Therefore, this study aims to relate fludarabine exposure during conditioning to the separate outcomes measures, using parametric cause-specific hazard models (CSH-models). Models were expanded with Markovian elements, by adding a transition from event to death for relapse and graft failure.

Subsequently, clinical trial simulations (CTS) were performed of studies comparing conventional dosing to alternative dosing strategies in the most abundant group of HCT recipients: adult leukemia and lymphoma patients. The aim of CTS was to estimate the expected survival as a result of reducing exposure variability, and to find the optimal design of a prospective confirmatory study in this patient group.

Methods:

Events considered were competing risks of graft failure, relapse, and NRM. Relapse was defined as disease recurrence, NRM as death while in complete remission. Both graft rejection and non-engraftment were considered graft failure.

Fludarabine cumulative area-under-the-curve for all doses ($AUC_{T0-\infty}$) was quantitatively linked to events using CSH-models.[9] For relapse, the transition to death was modelled using a parametric survival model

describing OS in relapsed patients with event-time as T0. For graft failure, a literature-derived 1-year-OS of 31% [10] was used as transition probability.

Optimal baseline hazards were selected per model. Covariates based on literature, as well as fludarabine $AUC_{T0-\infty}$, were evaluated as predictors. Evaluation of covariates was done by stepwise forward inclusion ($p<0.15$) and backward deletion ($p>0.05$). Continuous covariates were tested linearly and as a polynomial spline (3, 4 and 5 degrees of freedom).

The $AUC_{T0-\infty}$ resulting in maximum EFS probability, estimated by exponentiating the sum of the cumulative hazard for separate events, was henceforth regarded as the optimal exposure.

CSH-models were evaluated for predicting both EFS and OS, using a visual predictive check (VPC). The 95% confidence intervals and means of 1000 simulations were compared to the observed Kaplan-Meier estimates of both EFS and OS.

For the CTS, 1) the conventional 160 mg/m2 dose was compared to 2) dosing based on the predicted clearance (Cl_{pred}) by the pharmacokinetic (PK) model[5] or 3) dosing based on therapeutic drug monitoring (TDM), both 2 and 3 targeted to the optimal exposure.

Patient variables were derived from an in-house database of HCT recipients (2005-2016). The PK model was used to derive individual exposures following the various dosing strategies and to simulate 5 observations (1, 4, 5, 6, 7-hour post-infusion) on day 1 as input for TDM. TDM samples were randomly excluded according to the previously observed distribution of missing samples.[5]

The CTS were used to 1) determine the optimal trial design (dosing strategy, primary outcome, number of subjects, stratification) and 2) calculate the expected results of such trial.

Using baseline characteristics and fludarabine $AUC_{T0-\infty}$, daily event probabilities were estimated with the CSH-models. Events and OS were then simulated up to 1 year. Trial endpoints were: cumulative incidence of events and OS as calculated by the Kaplan-Meier method. To compare dosing strategies, p-values were calculated using Gray's test (events) or the log-rank test (OS). Power was defined as the percentage of studies with p less than 0.05. The design resulting in at least 80% power with minimal subjects was considered optimal. During trial optimization, 100 trials were simulated per design and the proposed optimal trial was simulated 1000 times.

Results:

The CSH-models were based on 192 patients. Models were best described by a log-logistic- (relapse), exponential- (graft failure), and Gompertz- (NRM & post-relapse survival) distribution. Fludarabine $AUC_{T0-\infty}$ was included on NRM (polynomial spline, 4 degrees of freedom, $p<0.001$) and graft failure (linear, $p=0.03$) hazards. The target $AUC_{T0-\infty}$ was found at 20 mg*h/L, with increased graft failures below, and NRM above this exposure. In the VPC's, simulated EFS and OS were in line with observations.

For CTS, 148 patients were selected. Missing data (weight/height: 33%) were imputed from the observed distribution per age quantile. 25 possible parameter vectors per subject were simulated with the PK model, to expand the dataset and account for uncertainty in expected clearance. Each derived set was then assessed as a new subject.

A design with 90 subjects randomized to either 160 mg/m^2 or TDM, stratified on renal function (≥ 90 ml/min/1.73 m^2) with NRM as a primary endpoint was found to be optimal. With a similar design, but Cl_{pred}-based dosing as a comparator, 80 more subjects per arm were necessary for sufficient power.

Simulations of the proposed optimal trial showed a decrease in median NRM from 27% in 160 mg/m2 dosing to 10% in TDM-based dosing. Relapse incidence and graft failure followed an inverse trend: there was 3% increase in relapse, due to more patients being at risk, and 2% more graft failures, as a result from the lower exposures following TDM-based dosing (median $AUC_{T0-\infty}$: 20 mg*h/L compared to 24 mg*h/L). Finally, OS increased from 57% (160 mg/m^2) to 72% (TDM-based), although the power for this result was only 63%.

Conclusions:

These results indicate that a substantial survival benefit may be achieved by individualizing the fludarabine dose prior to HCT. However, unpredicted variability and concomitant sub-/supra-optimal exposures in alternative dosing regimens decrease the power of a confirmatory trial for this effect. Therefore, TDM should be used as a comparator, to minimize remaining variability, and at least 90 patients per arm are necessary.

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C-04: *Gustaf Wellhagen* A bounded integer model for rating and composite scale data

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Objectives: Many clinical endpoints of importance for assessing the efficacy of therapy are obtained from rating or composite scales. Given the complexity of their nature, there is no fully satisfactory modelling strategy for such scale-based outcomes. Most commonly, these are treated as continuous variables (CV) but with the well-recognized problem that the underlying data are not continuous in nature and that data at the scale boundaries can not be well captured. An alternative modelling strategy is to treat data as ordered categorical (OC), but this approach has the drawback of requiring as many parameters, save one, as the number of categories in the scale already to describe the baseline characteristics. The aim of this work was to develop a new model for describing rating and composite scale data in a parsimonious way, while respecting the integer nature of the data.

Methods: For a scale with n categories the probit function, which is symmetric around 0, is used to divide the space under a standard normal distribution N(0,1) into n equally sized areas through n-1 cut-off values ($Z_{1/n}$ to $Z_{(n-1)/n}$). To define the bounded integer (BI) model, the probability for each category is estimated from a distribution N(f(t), g(t)) where both are a function of fixed and random effects, time and covariates (f(Θ,η,t,X)) and (g(σ,η,t,X)).

This BI model was implemented on an 11-point Likert rating scale data for pain [1] and different composite scale data: Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale, Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and Schizophrenia Positive and Negative Syndrome Scale (PANSS). The results of the BI model analyses were compared to previously published or corresponding OC and/or CV models for these data. See Table 1 for additional details on composite scale data and models.

Additional explorations were performed based on UPDRS data: (i) using simulations from a previously developed item response theory (IRT) model for UPDRS [2] we investigated the relationship between the IRT model characteristics and corresponding BI and CV models, and (ii) while it is natural to set the number of categories for the BI model to the number of categories of the scale as this would allow, in principle, extrapolation to any possible score, a more restricted number of categories, limited by the observed range, could be hypothesized to provide a better fit to data.

Results: The final BI model for the Likert example had a better description of the data than previously published models for these data. The OFV of the final BI model was 47492 with 14 estimated parameters compared to treating the data as OC (48902; 18) [1]. A published CV model [3] for the same data used only 9 parameters. When BI model was reduced to 9 parameters implementing the same structural, covariate and variability components, it performed better (53135) than the published CV model (55080) respectively. The runtime was shorter for the BI model compared to both CV and OC models. For the Likert data, the published OC and CV models contained components for serial correlation (Markov or autoregressive) and so did the developed BI models. However, also without serial correlation, the BI model performed better than corresponding CV and OC models.

The results for the composite scale examples are summarized in Table 1. In all cases did the CV model have a shorter runtime compared to the BI model.

Table 1. A comparison between BI and CV models for composite scale data.

Disease	Scale	Categories	Observed range	#Patients	#Obs	#Parameters	?OFV	Reference
						CV = BI	CV-BI	
Parkinsons's disease	UPDRS motor	109	0-80	19	946	16	113	[4]
Parkinsons's disease	UPDRS motor	133*	1-77	428	2720	14	73	[2]
Alzheimer's disease	ADAS-Cog	71	0-70	817	3594	11	730	[5]
Schizophrenia	PANSS	181	30-176	1323	7728	17	145	[6]
Schizophrenia	PANSS	181	30-167	1292	8520	15	17	[7]

* The UPDRS scale was revised in 2007

Simulations from the IRT model for UPDRS predicted that the residual variability (σ) for the CV model and g(t) for the BI model, varied depending on the underlying disability. However, the predicted variability in the latter was considerably lower. Also, a linear change in the IRT disability mapped in most of the assessed range to a linear change in the BI model, but a rather nonlinear (sigmoid) change in the CV model.

BI models for UPDRS using the full scale range (0-133) or only the observed range (0-80), had the same number of parameters and similar goodness-of-fit (OFV) to data.

Conclusions: The bounded integer model provides a good description of rating and composite scale data, both in terms of fit and simulating real-life like data. It has consistently shown better fit than models treating the same data as either ordered categorical or a continuous variable. The BI model has advantages over OC models because it is parsimonious in number of estimated parameters and because it can be used to predict categories not present in the data (both interpolation and extrapolation). Additionally, the possibilities for parsimonious description of variability in observed in data appear to be more easily implemented in these probit-based, as opposed to logit-based, models.

While BI models do not use more parameters than CV models, they respect the integer nature of the data and the scale boundaries. A standard CV model will predict values outside the expected range due to variability or, if e.g. logit transformation or beta regression is used, will only predict the extremes scores asymptotically. Avoiding such model misspecification will provide a more robust basis for model inference and simulation. The only expense is a longer runtime of BI models, but for all the presented examples this was no more than about one hour on a single node.

The BI and the IRT models both respect the underlying non-continuous nature of data and the similarity of the two model types is not surprising given that both operate on a similar latent variable scale. Future explorations plan to further explore the nature of the relationship between these two models and the possibility to make joint analyses of total score and item level data.

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C-07: *Phyllis Chan* Assessment of a model to correlate early tumor size response to overall survival in relapsed or refractory diffuse large B cell lymphoma patients

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Objectives: To use tumor size metrics measured during treatment to predict overall survival (OS) in patients with relapsed or refractory diffuse large B-cell lymphoma (*R/R DLBCL*), as a potential approach to enable early decision making [1].

Methods: A sequential approach was used for model development. Longitudinal measurements of tumor size (square root of sum of product of diameters [SPD] of the target lesions) from 190 patients in two polatuzumab vedotin clinical trials (GO27834/NCT01691898 and GO29365/NCT02257567 [2-5]) were characterized by four tumor growth inhibition (TGI) models. The models comprised the simplified TGI model [6], Stein model [7], modified Stein model (using different shrinkage rate parameters to describe the treatment phase and post-treatment follow-up phase), and Chatterjee model [8]. Clinically relevant baseline covariates were assessed for their effect on the TGI model parameters, including tumor SPD at baseline, tumor growth, and shrinkage parameters, using univariate screening and backward elimination. Then a TGI-OS model describing the correlation between TGI model-derived parameters and OS was developed. The final model was determined by the following process: model-estimated tumor metrics and pre-specified clinically-relevant baseline covariates were screened as prognostic factors for OS by univariate Cox-proportional hazard models, based on the criterion of p-value < 0.005; next, backward elimination was applied on the selected prognostic factors, with selection criterion p-value < 0.001, in order to establish the final model using parametric survival analysis. Treatment group was evaluated as a covariate for both the TGI and the TGI-OS models. Model qualification was conducted through posterior predictive checks.

Results: Longitudinal tumor size data were adequately described by the four TGI models. The modified Stein model with normal distribution of shrinkage rate after the end of treatment was determined to be the best, based on the Bayesian Information Criterion. Statistically significant covariates included the effects of baseline lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status, and bulky disease on baseline tumor size. Treatment group was not a statistically significant covariate in the univariate screening step.

Based on univariate Cox model, among the TGI model-derived parameters, the tumor growth rate (KG), baseline tumor SPD, and week 8 to baseline tumor ratio (TR8) were most highly correlated with OS (p-values < 10^{-5}), with KG being the most statistically significant predictor. Higher KG, baseline tumor SPD, and TR8 were all associated with shorter OS. Posterior predictive check plots stratified by KG or TR8 quartiles and baseline covariate categories (e.g. quartiles of time from most recent therapy to study start, LDH, hemoglobin, ECOG status, presence of bulky disease, age) showed that the prediction intervals simulated from the final TGI-OS model correspond well with the observed Kaplan-Meier curves pooled from the two studies. For the baseline covariates, increased model-estimated baseline tumor size was associated with shorter OS. No other statistically significant covariates, including treatment group, were identified for the TGI-OS model.

Individual patient KG or TR8 estimated from the final TGI model that incorporated multiple statistically significant covariates were compared directly among the six treatment groups in these two studies, and p-values from t-tests comparing two samples at a time indicated two treatment groups to be less effective than the other four treatment groups. These results showed TGI-based efficacy comparison between treatment groups is consistent with the comparison based on response criteria for malignant lymphoma [9].

Conclusions: This analysis demonstrated that model-estimated tumor-size metrics such as KG estimated from the TGI model, as early as 8 weeks after start of treatment, could be of value to predict OS. Both the TGI and TGI-OS model are treatment-group independent, which allow comparison of efficacy across different treatment groups based on TGI metrics.

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C-08: *Rui Zhu* Exposure-response (E-R)-based product-profile (PP)-driven clinical utility index (CUI) to support phase III dose selection in oncology

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Introduction/Objectives:
Benefit-risk assessment of a therapeutic agent can support decision-making in both drug development and regulatory evaluation. The traditional way of assessing benefit-risk involves characterizing dose/exposure-response relationships on primary efficacy and safety endpoints separately and then qualitatively comparing those relationships to support decision-making of dose/formulation selection, go/no go in clinical development, etc. However, with this implicit approach, it is difficult to balance benefit with risk when there are multiple important attributes. Therefore, the CUI, a more structured quantitative approach that brings all the attributes onto the same scale and reduces them to a single measure, allows more transparent and efficient benefit-risk assessment and decision-making [1-4].

The aims of this work were to characterize ipatasertib E-R relationships in a phase II study and to quantitatively assess benefit-risk using the CUI approach to support ipatasertib phase III dose selection in combination with abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC).

Methods:
Data used in the analyses were from a double-blinded, randomized phase II part of a phase Ib/II clinical trial, where patients (n=253) received placebo, or ipatasertib 200 mg or 400 mg daily in combination with abiraterone [5]. Logistic regression and Cox proportional-hazards models characterized E-R relationships for safety (various adverse events [AEs]) and efficacy (radiographic progression-free survival [rPFS]) endpoints, respectively. To capture the effect of dose modifications, an exposure metric based on the actual dosing (AUCactual) was used in the E-R modeling. Dose-intensity (DI) models were developed to characterize the DI relationship across treatment arms. E-R models were coupled with their corresponding DI models to project the dose-response relationships over the range of 0 to 500 mg daily ipatasertib dose. In addition, E-R analyses and dose-response projections with (AUCactual) and without (AUC based on planned dose [AUCplanned]) considering dose modifications were compared. A utility measure was developed for each important safety or efficacy attribute selected based on ipatasertib PPs, and they were weighted and combined for the CUI calculation. Combined results from overall utility profiles and probability of reaching PP utility levels were used to determine the dose with optimal benefit-risk balance.

Results:
The E-R analysis of the rPFS hazard ratio (HR) demonstrated a statistically non-significant ($P>0.05$) association between ipatasertib exposure and rPFS HR, with a slight trend of higher exposure leading to a lower rPFS HR. The E-R analyses of AEs indicated a statistically significant ($P<0.05$) association between exposure and AEs tested. The probability of having AEs of various grades increased with increasing exposure. Comparison between the E-R relationships from models with AUCactual and AUCplanned indicated that the E-R trends were generally flatter in the latter, but the dose-response projections from both models were very similar with slightly larger variability in the latter.
Based on the PPs, rPFS HR, diarrhea, and rash were selected as key attributes with cutoff/tradeoff values. Given the AEs are generally manageable and reversible, a slightly higher weight was chosen for efficacy

(0.6) than for AEs (diarrhea [0.3] plus rash [0.1]). Sensitivity analyses were conducted to test the following 4 pre-defined scenarios: (1) weight assignment for rPFS:diarrhea:rash=0.6:0.3:0.1, grade ≥2 AEs, (2) 0.6:0.3:0.1, grade ≥3 AEs, (3) excluding rash with 0.6:0.4:0, grade ≥2 diarrhea, and (4) excluding rash with 0.6:0.4:0, grade ≥3 diarrhea. Results from all 4 scenarios supported 400 mg daily as the optimal dose.

Conclusions:
This E-R-based PP-driven CUI framework may be useful to support dose selection in clinical drug development with multiple attributes to balance. In practice, pre-defined PP can be a good anchor point to help team reach agreement on the key components for CUI analysis, eg, important attributes, weights, and clinically-meaningful cutoff/tradeoff values. Comparison of E-R modeling and simulation results from exposure metrics with and without considering dose modifications can be used to guide exposure metric selection in E-R analyses in trials with sizable dose modifications.

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C-09: *Zinnia Parra-Guillen* A quantitative modelling framework to inform dose selection of Xentuzumab, a dual insulin-like growth factor-I/II neutralizing antibody in cancer patients

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Objectives: Over the past decade, the insulin-like growth factor (IGF)-signalling pathway has gained substantial interest as a potential new therapeutic target in oncology [1]. Xentuzumab is a humanised IgG1 monoclonal antibody (mAb) binding both IGF-I and IGF-II and thereby inhibiting downstream signalling essential for survival and tumour growth. This pathway is further regulated via binding of IGFs to circulating binding proteins (BPs). The aim of the current work was to develop a mechanistic model characterising the dynamics and interactions of IGF-I, IGF-II, BPs and Xentuzumab to guide dose selection during clinical development.

Methods: To build and validate the mathematical model, in house *in vitro* studies, literature and clinical data were used. Time courses of IGF-I (total and free) and their main binding protein BP-3 (total and bound) in plasma were obtained from literature [2-4]. Clinical data came from two phase I studies, where Xentuzumab doses of 10-1800 mg weekly or 10-3600 mg every 3 weeks were administered to advanced solid cancer patients (n=125). Within these trials, total IGF-I, IGF-II, BP-3 and Xentuzumab plasma concentrations were measured over time. Part of the clinical data from the higher doses was saved for model validation (n=50 for pharmacokinetics and n = 59 for pharmacodynamics). Model development was performed in three steps: (i) population pharmacokinetic analysis of Xentuzumab, (ii) modelling of the biological system representing endogenous IGF-I, IGF-II and BPs in the absence of drug accounting for synthesis, degradation and binding processes of the free and bound entities, and (iii) integration of the two previous models to characterise IGFs and BPs dynamics during Xentuzumab treatment. Quasi steady-state equilibrium was assumed to compute baseline conditions. A molar excess of BPs over measured BP-3 (characterised by the parameter FACBP) was assumed and optimised during model building. Model calibration was undertaken by comparing model predictions with real data. The final model was used to predict neutralization of free IGF levels at trough steady-state (t=6 weeks) for different Xentuzumab doses and dosing schedules to support Phase II dose selection. A sensitivity analysis evaluated the impact of final model parameters on the predicted neutralization of free IGFs for the selected dosing regimen. Analyses were performed in NONMEM 7.3 and MATLAB.

Results: An adequate description of all evaluated scenarios from literature and clinical data (including training and validation set) was obtained with the final model. Simulations showed that in order to achieve > 90% neutralization of free IGF-I at trough steady-state, a 1000 mg weekly dose was needed. Simultaneously, >64% neutralization of free IGF-II was estimated (higher uncertainty due to limited knowledge on free IGF-II from literature). Interestingly, equivalent total doses administered less frequently (i.e. 2000 mg every 2 weeks or 3000 mg every 3 weeks) resulted in lower IGF neutralization compared to weekly administration, suggesting that over-proportional doses would be needed to obtain the same effect. During the sensitivity analysis, FACBP appeared to be the most influential parameter, as a drop of only 10% translated into more than double levels of free IGF at steady state. However, when looking at the % of IGF neutralization, FACBP values ranging from 1.1 to 1.5 (plausible interval) translated into a minor change in

the predicted inhibition of free IGF-I and IGF-II at steady state of 88-91% and 56-66%, respectively, suggesting model robustness.

Conclusions: A mechanistic model solving multiple protein interactions has been developed to characterise the disposition of IGF-I, IGF-II and BPs in the absence and presence of Xentuzumab. The quantitative framework allowed us to predict the time-course of unmeasured markers in Xentuzumab treated cancer patients, particularly plasma concentrations of free IGF-I and IGF-II as ultimate drug targets. The Xentuzumab dose of 1000 mg/week was finally selected as recommended Phase II dose supported by the model predictions of % free IGF neutralization, illustrating the utility of systems pharmacology type models beyond target identification.

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C-12: *Scott Pruitt* Clinical Overview of Immunotherapy in Oncology

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Overview/Description of presentation:

The concept of harnessing the immune system to fight cancer is not new, but only recently have immunomodulatory pharmaceutical agents been developed that show clear clinical benefit for the treatment of cancer. Following studies of anti-CTLA4 mAb monotherapy and cell-based Provenge, in melanoma and prostate cancer, respectively, which demonstrated that immunotherapy was clinically efficacious, attention has turned to multiple different strategies to stimulate anti-tumor immunity.

Clinically approved approaches to cancer immunotherapy currently include CART-T cell therapy and oncolytic virus injection, but arguably the most important approach is blockade of the PD-1/PD-L1 immuno-inhibitory pathway. Anti-PD1 mAbs pembrolizumab and nivolumab, as wells as other, have been approved as monotherapy in multiple indications, in many cases based on objective response rate (ORR) results from single arm trials.

While tumor expression of PD-L1, assessed by immunohistochemical staining, is predictive of response to PD-1/PD-L1 blockade in a variety of tumor types, also under active exploration are multiple other potentially predictive biomarkers, including tumor microsatellite instability-high (MSI-H). Pembrolizumab recently received the first tumor type agnostic biomarker-based approval for the treatment of any tumor found to be MSI-H. This unique USFDA approval was based on data from multiple single arm trials, including a rare tumor basket trial, and local biomarker testing.

Anti-PD-1/PD-L1 mAb monotherapy continues to be evaluated in multiple indications and remains the foundation for cancer immunotherapy, but many current trials are evaluating the additional of second agents in combination with PD-1/PD-L1 blockade. The combination of nivolumab + anti-CTLA4 mAb, for example, remains under active investigation, while the combination of pembrolizumab + chemotherapy is showing clinical promise in multiple indications. In contrast, results from studies evaluating the combination of pembrolizumab + the IDO1 inhibitor epacadostat have begun to be reported, with no additive benefit of the combination over pembrolizumab monotherapy recently reported in melanoma, despite early phase clinical studies that suggested promising clinical anti-tumor activity with this combination. Triple combination therapies, again with PD-1/PD-L1 blockade as the common foundation, are being evaluated in clinical trials, some of which are utilizing an umbrella trial design approach to potentially allow efficient signal finding for multiple different combination therapies within a specific tumor indication.

A major challenge remains over how, in Phase 1b/2 studies, to identify promising combinations that have enhanced efficacy over PD-1/PD-L1 blockage alone and therefore warrant further clinical investigation. It is also not clear if the unique paradigm of accelerated approval based on single arm trial data with a subsequent confirmatory pivotal study will be acceptable for such combinations of multiple agents or whether the “combination rule” will require larger multiple arm studies that in turn would delay access of dying cancer patients to potentially effective immunotherapy combination regimens.

Conclusions/Take home message:

The field of tumor immunotherapy is rapidly evolving, necessitating novel approaches to regulatory approvals, signal finding studies, and potentially predictive biomarkers.

C-13: *Benjamin Ribba* Drug response variability and optimal dosing in immuno-oncology

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Objectives: Present some aspect of the biology and mechanistic PK/PD modelling, including clear applications in the early clinical space driving dose, regimen and possibly combination selection

Overview/Description of presentation: Leveraging, through quantitative methods, the time-course of tumour size and biomarker in oncology has been shown to be a relevant approach to avoid unnecessary toxicity, improve efficiency of active drugs, thus enabling an optimization of resource spending in patient care.

Immuno-oncology (IO) is becoming established as one of the main areas of focus for drug development. Early clinical findings indicate that a patient's response to IO mostly depends on their immune system functions. For instance, expression of programmed-death ligand 1 (PD-L1) in tumour tissue appears to correlate positively to melanoma patients' clinical response to nivolumab; and the inter-patient variability in immune function is viewed as a major factor to explain the differences in the timing of tumour response to ipilimumab. In addition, results have indicated that the immune factors associated with clinical response to ipilimumab and nivolumab in monotherapy might not translate to combinations. It is thus plausible that "fishing" for markers of efficacy, without being guided by a comprehensive and quantitative view of the immune system, is not the most efficient approach to successful IO drug development.

Developing computational models of the immune system in the context of IO can be viewed as a valuable tool to better explore the role of disease heterogeneity and to improve the identification of responders and the design of clinical trials. From a computational model of the immune system, many different treatment options and schedules can be simulated and the timing of biomarker sampling can be optimized to enhance the values of the experimentation.

Conclusions/Take home message: While leveraging early clinical data through the modelling the immune system represents a technological-demanding shift from the traditional way of analysing early clinical data, it can also represent a valid opportunity; for which each decision maker should pay attention, to assess the potential value to better support the clinical development of IO drugs.

C-15: *Rukmini Kumar* Predicting response and identifying responders to combination cancer immunotherapy in melanoma using Quantitative Systems Pharmacology (QSP) models

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Introduction:

QSP models at various levels of physiological detail can support decision making in various stages of the cancer immunotherapy pipeline, from early discovery to clinical development. We have developed models of immune-mediated tumor killing, calibrated the model to two immune therapies, and used it to predict response to combination therapy. Further, we have used the model to identify key patient characteristics of responders to double immune combination therapy.

Objectives:

* Develop QSP model of appropriate physiological detail to address various questions in a Cancer Immunotherapy drug development program

* Use model to predict characteristics of melanoma patients that benefit from combination of two immune therapies.

Methods:

QSP model development was initiated by extensive review of the public literature describing clinical observations and the mechanistic drivers of immune-mediated tumor killing. The model was first calibrated to a therapy that converted incactive CD8s to active CD8s in the tumor then expanded to include therapy that increases CD8 density in the tumor. The model has five ordinary differential equations that capture the growing tumor, as well as aspects of the immune system such as activated and inactivated cytotoxic CD8 T cells, 'lumped' pool of pro-inflammatory (T helper) and anti-inflammatory (T Regulators) cell types. Each Virtual Patient (VP) has five Virtual Tumors ('target lesions' for RECIST scoring). Post treatment change in the sum of tumor diameters, as well as stochastic simulation of non-target lesion and new metastatic lesions are used to generate RECISTv1.1 scores. The model parameters are constrained directly by literature when data is available, or constrained to match published clinical data, and these are documented.

Results:

A Virtual Population (VPop) was calibrated to publicly available clinical data on immune monotherapy. The mechanistic tumor dynamic model was calibrated to observed changes in the sum of longest tumor diameter (waterfall plots) such that 20% or more of VPs showed greater than 20% increase in tumor diameter). The stochastic model was then calibrated to reflect greater than 40% of patients with progressive disease (via RECISTv1.1), some despite reduced target tumor mass (due to new metastatic lesions, non-target growth or rebound). Other aspects of published clinical characteristics such as baseline distribution of density of immune cells (Percent Tumor Infiltrating Cells are < 20% of total cells in tumor),

baseline tumor size distribution, and change in CD8 cell densities on therapy (median of 2 fold increase from baseline) were also matched. Rates of metastases, within patient correlation of Percent Tumor Infiltrating Cells, killing rate and other parameters that were not constrained directly by data were estimated in the calibration process.

Simulation of combination therapy predicted dramatic reduction in tumor mass typified by waterfall plots but more modest improvements in RECIST scores. For the most part, both immune therapies were predicted to be effective in tumors that were inflamed prior to therapy. Non-inflamed tumors were predicted to be non-responsive to either monotherapy or the combination. However, there is a subset of virtual patients that responded to the combination but neither monotherapy. These VPs were found to have modest infiltration of immune cells, or lower levels of the T helper cells at baseline.

Conclusions:

While there is great excitement around the prospects of double immune therapy, these combinations are unlikely to be effective in "cold" tumors that are not recognized by the immune system. Significant expansion of the responder population may require therapy directed at stimulating an immune response (making tumors "visible" to the immune system) rather than adding to a pre-existing immune response. QSP models can be effectively used for patient stratification in Cancer Immunotherapy combination programs.

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C-16: *Hanna Silber Baumann* PKPD analysis of soluble CD25 to characterize the concentration-effect relationship observed following the administration of Cergutuzumab Amunaleukin, a targeted immunocytokine for cancer immunotherapy

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Objectives: 1. To quantify the concentration-effect relationship of Cergutuzumab Amunaleukin (CA) on the plasma pharmacodynamics (PD) marker soluble CD25 (sCD25), and 2. To support optimization of the dosing regimen of CA by investigating the impact of alternative dosing regimens on sCD25 through simulations.

Methods:

CA is a novel monomeric Carcino Embryonic Antigen (CEA) targeted immunocytokine where a single, engineered IL-2 variant (IL2v) with abolished IL2-Rα (CD25) binding is fused to the C-terminus of a high affinity anti-CEA antibody. Such a molecular design aims to expand CD8 T cells and NK cells while avoiding preferential expansion of regulatory T cells. CD25 is the IL2-Rα unit of the IL-2 receptor and is expressed on activated CD8 T cells as well as on regulatory T cells. sCD25 is shed from proliferating immune cells and has been identified as a marker of peripheral immune activation and possibly efficacy [1].
CA is currently being investigated in early clinical development in solid tumors. In humans, CA displays complex pharmacokinetic (PK) behavior; a model describing the target mediated drug distribution (TMDD) and expansion of the target pool has been presented previously [2,3].
Data from an entry-into human dose escalation study was used for this PKPD analysis. Patients received escalating doses of 0.1-40 mg of CA in weekly (QW) or bi-weekly (Q2W) cycles. sCD25 was sampled up to 4 or 5 cycles for the Q2W and QW regimens, respectively. Patients had on average 8 sCD25 samples, and the PKPD database was composed of 104 patients.
The analysis was performed using NONMEM7.3. A stepwise model development was performed. The parameters of the PK model were kept fixed during the development of the PD model.
Simulations were performed to investigate how the sCD25 profiles can be impacted by different dosing regimens including dose up-titration, induction-maintenance regimens combining QW and Q2W dosing as well as less frequent dosing regimens such as Q3W or Q4W dosing.

Results:

The initial graphical analysis indicated that the expansion of sCD25 was stronger with the QW regimen compared to the Q2W regimen following the initial 4-5 CA administrations, in agreement with the observed immune cell expansion pattern. Following multiple dosing, the magnitude of sCD25 expansion on each cycle was diminished when compared to each pre-dose concentration. This result was in line with the underlying complex PK which results in an expansion of the target pool with an increased clearance and reduced exposure of CA following multiple dosing.
sCD25 was well described using an indirect response (IDR) model with the drug stimulating sCD25 production rate (i.e. shedding). An effect compartment was included to further capture the delay between CA concentrations and the resulting sCD25 profile. The drug effect was best described by a sigmoid Emax model. The parameters of the IDR model were estimated with good precision (RSE<25% for population parameters; RSE<50% for IIV). The proportional residual error was 17% and the IIV ranged between 26 and

60%. The baseline value of sCD25 was incorporated as a covariate on Emax. The model indicated that close to maximum effect would be reached with a well-tolerated dose (15 mg) on cycle 1.
The simulations showed that sCD25 could initially be expanded to higher concentrations with a QW regimen compared to less intense regimens, but that these high concentrations could not be sustained due to the simultaneous induction of clearance by the target cells leading to reduced drug exposure. With a less intense regimen, the sCD25 would reach a new steady state after a few administrations that would be higher than with the QW regimen.

Conclusions: A PKPD model was developed to describe the sCD25 concentration time course upon CA dosing. The model was able to capture the observed exposure-response pattern and was used to support the exploration of additional dosing regimens in the clinic.

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D-01: *David Ternant* Population and Bayesian kinetic modelling of necrosis biomarkers to assess the effect of conditioning therapies on infarct size

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Objectives: Infact size is a major predictor of subsequent cardiovascular event following ST-segment elevation myocardial infarction (STEMI). It is frequently used in clinical trials focused on cardioprotection. Imaging techniques, as cardiac magnetic resonance imaging, accurately measure infarct size but are of limited availability. Therefore, prediction of infarct size is often assessed using repeated blood sampling and the estimation of area under the concentration curve (AUC) of biomarkers, as total creatine phosphokinase (CK), myocardal band CK (CK-MB) and troponin I (cTnI). However, the performance of AUC to estimate infarct size is limited, because is blurred by interindividual variability in input, distribution and elimination rates of biomarkers. This work aimed at (i) building models allowing the estimation of the necrose biomarker amount released by lesion using population compartimental analysis, (ii) investigating the relevance of biomarker amount and (i) developing limited sampling strategies (LSS) allowing accurate biomarker amount estimates using Bayesian anlysis.

Methods: Three population kinetic biomarker amount estimators were developed for CK, CK-MB and cTnI biomarkers. Repeated biomarker concentrations measurements were obtained from five clinical trials evaluating the impact of conditioning therapies in STEMI between 2005 and 2013 [1-5] . For each patient, 13 to 15 biomarker repeated measurements between hours 0 and 72 after inclusion were available. Patients were randomly assigned to learning (2/3) or validation (1/3) subsets. Using learning subset: 1 or 2 compartment population kinetic models with 1 or 2 gamma distribution functions for biomarker input, and zero and/or first-order transfer distribution and elimination rate constants were built; Bayesian LSS estimators including 1, 2 and 3 samples were developed. Predictive performances of LSS estimators were compared using both learning and validation subsets.

Results: Among clinical trials, 132 patients were evaluable for CK and cTnI, and 49 patients for CK-MB. CK and cTnI kinetics were best described using 2 compartment models, whereas 1 compartment was sufficient for CK-MB. Two gamma distribution functions were necessary for cTnI input rate, whereas 1 distribution was sufficient for CK and CK-MB input. Our kinetic models provided accurate estimations of biomarker release input and powerful assessment of conditioning treatment. Short sampling (within 24 hours after inclusion) was possible for LSS estimators. Three-sample LSS provided best prediction accuracies (R^2 > 95%). For CK-MB, sampling times 8, 16 and 20 hours was the best LSS.

Conclusions: Accurate estimations for biomarker input and powerful assessment of conditioning therapies were obtained using a limited number of samples taken within 24 hours after inclusion. This « more powerful and less expensive » strategy will certainly be a useful add-on to future studies in the fild of STEMI and cardioprotection.

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D-02: *João Abrantes* Integrated modelling of factor VIII activity kinetics, occurrence of bleeds and individual characteristics in haemophilia A patients using a full random effects modelling (FREM) approach

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Objectives: Haemophilia A (HA) is a bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII). Although model-based TDM of FVIII products has been encouraged [1], there is still a lack of knowledge on the exposure-response relationship, and therefore on the individual FVIII activity level to target.

In this study, we aimed to develop an integrated pharmacometric model to characterize the relationship between FVIII activity and occurrence of bleeding episodes in HA patients receiving prophylactic treatment, accounting for all available patient and study specific characteristics.

Methods: Pooled pharmacokinetic (PK) and bleeding data during prophylactic treatment with BAY 81-8973 (octocog alfa, Kovaltry®) were obtained from the three LEOPOLD trials [2-4]. The studies had a duration of 6-12 months and included previously treated patients aged 1-65 years. Available patient characteristics were age, weight, body mass index, lean body weight, race, von Willebrand factor levels, number of bleeds in 12 months pre-study (NBL), previous therapy history (on-demand/prophylaxis) and number of target joints at study start.

Initially we evaluated previously developed popPK [5] and parametric repeated-to-event (RTTE) models [6]. The RTTE model was re-estimated including bleeding data from the LEOPOLD kids trial (age ≤12 years), and alternative baseline hazard [$h_0(t)$] parameterizations and different inter-individual variability (IIV) model structures were explored. In addition, the inclusion of a time-dependency between consecutive bleeds was tested with a Markov hazard rate accounting for the time since the last event (TSE), implemented as an exponential term, $\lambda_{markov} \cdot e^{-\gamma\ markov \cdot TSE}$. At study start, 1/NBL was used as an estimate of TSE. The PK model was qualified through GOF plots and stratified pcVPCs, and the RTTE model with stratified VPCs of the Kaplan-Meier (KM) curves and KM mean covariate plots. Parameter uncertainty was estimated with SIR.

The updated models were converted to a FREM model [7,8], with all patient characteristics available treated as observations, and all parameter-covariate relationships estimated simultaneously using exponential and power relations. Modelling was performed in NONMEM 7.3 employing the IMPMAP method, assisted by PsN and graphical and statistical analyses by R.

Results: The final FREM model included 1535 FVIII activity observations (N=183 patients; more details on PK sampling design [5]), 663 bleeds (N=172), and 11 individual characteristics.

The previous popPK model was appropriate, however IIV on the residual error further improved the fit ($p<0.001$) and increased parameter precision, and was therefore included. The drug effect was included on the hazard ($p<0.001$) described by $h(t) = \lambda \cdot e^{\gamma \cdot (t-1)} \cdot (1 - FVIII/(FVIII+IF50))$, with log-normal IIV on the scale parameter (λ). Both λ and IF50 (FVIII activity resulting in half-maximum inhibition) were parametrized in terms of $\lambda_{0.5}$ and λ_{20} at 1 year after study start, representing the hazard when plasma FVIII activity was 0.5

IU/dL (severe HA) and 20 IU/dL (mild HA), respectively. There was no evidence that a bleeding episode transiently changed the hazard of a new bleed (p>0.05 for markov component). The final parameter estimates were $\lambda_{0.5}$=2.9 year^{-1} [95%CI 1.9,3.9], λ_{20}=1.1 year^{-1} [0.72,1.4], γ=-0.56 year^{-1} [-0.85,-0.28], and IIV on λ 167%CV [110,225], and the derived IF50 was 11 IU/dL.

The full covariance matrix included the interaction between CL, V, hazard (λ), residual error magnitude and 14 covariates. The parameter-covariate relationship showing the largest effect size was NBL on hazard of bleeding; a patient with 1 bleed one year pre-study had a 24% [-35,-12] lower hazard compared to a patient who had 21 bleeds (mean), and a patient with 84 bleeds had a 144% [51,300] higher hazard. The inclusion of all covariates in the model resulted in a maximum IIV (CV%) drop of 5.7 CL, 1.5 V and 11 λ.

Conclusions: We developed a model describing FVIII activity and occurrence of bleeds over time in adult and paediatric HA patients during prophylaxis, accounting for all available individual characteristics. Plasma FVIII activity and the number of previous bleeds were found to be the main factors predicting the bleeding risk. The developed model may lead to a more effective and cost-efficient dosing in haemophilia A.

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D-03: *Elin Boger* A partial differential equation approach to inhalation PBPK modelling

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Objectives:

Inhalation pharmacokinetics (PK) is known to be vastly complex due to the spatial heterogeneity in lung physiology and the range of processes affecting pulmonary drug disposition. Further complexity is added from the difficulty associated with measuring relevant concentrations, i.e. the local concentration(s) driving the pharmacological effect. Hence, it is non-trivial to predict and evaluate how various design decisions will affect the PK, and ultimately the pharmacodynamics (PD) of locally acting inhaled drugs. In the absence of relevant measurements, mechanistic modelling becomes even more critical. However, although some inhalation PBPK models accommodate all main features of inhaled drug disposition, these do not include a high-resolution model of both transport (mucociliary clearance) and shrinkage (dissolution) of polydisperse particles at high resolution. This study therefore aimed to develop the first high resolution model accounting for all main pulmonary drug disposition processes as well as the heterogeneity in physiology and particle size.

Methods:

The first inhalation PBPK model utilizing partial differential equations (PDEs) for describing dissolving particles of varying size over the depth of the lung was developed. The lung is further described by three states varying over the lung depth: 1) epithelial lining fluid, 2) epithelium, and 3) sub-epithelium. The model mechanistically describes important processes for pulmonary drug disposition, including regional drug deposition, particle dissolution and mucociliary clearance. Furthermore, by reducing the system to a one dimensional PDE and addressing the numerical issues encountered when simulating shrinking particles in other models [1-2], the computational cost is significantly reduced without any loss of accuracy.

Results:

In multiple case studies, we demonstrate important features of the model and evaluate how different design decisions affect the target site concentration(s). Furthermore, we also explore how changes in these concentrations are reflected by measurements from observable states. That is, the model can theoretically explore *if* and *how* contemporary sampling techniques will reflect the dynamics of the target site concentration(s).

For instance, the particle size distribution (PSD) is highlighted as an important design parameter, both for regional lung-targeting and duration. For poorly soluble compounds, simulations show that larger PSDs provide longer drug coverage at the target as compared to smaller PSDs. However, this comes at the expense of lower drug levels. Smaller PSDs have previously been demonstrated to achieve a higher and earlier plasma peak compared to larger particles [4], a behavior that was reproduced by our simulations.

In all case studies, a spectrum of free concentrations is predicted to arise along the lung with distinct differences between the epithelial and sub-epithelial layer. Additionally, simulations indicate that the

advantage of inhalation can be almost eradicated if the inhaled dose is high enough. Interestingly, this occurs already at dose levels where nonlinearities would be challenging to detect from the measurable plasma concentrations.

Conclusions:

The presented model can be used for guiding the design of inhaled molecules and PSDs. Furthermore, it can aid the design and interpretation of preclinical/clinical studies. Its high spatial resolution provides opportunities to explore regional lung-targeting. The importance of highly spatially resolved simulations is further highlighted as predictions indicate that a spectrum of free drug concentrations spans the lung after inhalation. This finding has interesting implications for PK/PD-modelling, as it suggests it is inappropriate to assume a single free concentration driving the pharmacological effect of locally acting inhaled drugs. Equally important, this result emphasizes that it is crucial to identify the pulmonary region(s) relevant for the effect to enable informed design decisions.

Interestingly, the simulations raise concerns about the utility of using plasma PK for evaluating the local effect and therapeutic ratio of inhaled drugs. Thus, prompting the need for utilizing mechanistic modelling and investing in identifying other sampling techniques. Furthermore, the mathematical description is general and may be extended to describe absorption from the gastrointestinal tract, where high level of discretization is still used [1, 4].

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D-04: *Chihiro Hasegawa* Simplification of multi-scale systems models for data-driven analyses: what has progressed in these 5 years?

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Objectives: Bridging multi-scale systems models and pharmacometrics has resulted in models that are highly complex and often not amenable to further exploration via estimation or design. Proper lumping has been used for order reduction of such complicated models. Using the technique, Gulati et al [1] successfully obtained a reduced version of the coagulation network model which describes the time course of fibrinogen recovery after a brown snake bite. However, the process was achieved heuristically since proper lumping cannot be explicitly performed for models described by nonlinear ODEs (common in systems pharmacology models), but the process can be applied directly to linear systems. The aim of this study is to systematically simplify a nonlinear systems model of bone biology [2] and then assess the performance of the simplified model by extrapolating improvement in long-term bone mineral density (BMD) responses from denosumab.

Methods: The methods were performed in two parts: (1) scale reduction of the bone biology model to accommodate the input target or denosumab (a RANKL inhibitor) and (2) the use of this model to analyse BMD data that arose from 1 year treatment with denosumab and then predict BMD of a further 4-year period. Part (1): the original system was first linearised using an inductive approximation in order that proper lumping can be fully applied [3]. Starting with the linearised original system, the best reduced model was searched using proper lumping together with a composite criterion consisting of two opposing indices, i.e. model performance and a penalty for complexity [4]. These were conducted using MATLAB R2015b. An identifiability analysis was conducted on the reduced model to assess parameter estimability. Part (2): the reduced (mechanistic) model and two empirical models were then “trained” (by parameter estimation) to BMD data following administration of denosumab for data over 1 year. Each model was then used to extrapolate the BMD response beyond 1 year. Data were extracted from [5]. Model fitting was conducted using NONMEM 7.3.0.

Results: A linearised version of the original nonlinear bone model was successfully obtained after 20 iterations of the linearisation process. Through proper lumping, the original 28-state original model was reduced to an 8-state model using an automated process based on choice of a weighting criterion value that balances model performance against model complexity. The reduced model described an increase in BMD after denosumab dosing which was indistinguishable from the original nonlinear bone model. The lumping process resulted in some of the states being lumped into either the RANK or RANKL state. Other states, e.g. RANK-RANKL complex and active TGB-beta, remained unlumped as in the original model. Lumping of these states significantly affected performance of the reduced model. Based on the identifiability analysis, 5 parameters were considered estimable. After fitting the reduced model to the BMD data until 1 year, the reduced model was able to be applied to extrapolate long-term BMD responses over 1 year. Both empirical models provided excellent fits to the 1 year BMD data but provided poor predictions when extrapolated beyond 1 year.

Conclusions: A scale of the nonlinear bone biology model was successfully reduced to an 8-state model by inductively linearising the system followed by automatic proper lumping. Importantly both the linearisation and lumping methods are reversible processes so that it is always possible to switch between full and

reduced and nonlinear and linear systems. The reduced model described an increase in BMD after denosumab dosing that was equivalent to the full model and was able to accurately predict BMD change when used for extrapolating to long-term responses. The method used in this study is automatic, and can be applied directly to other multi-scale models for developing a mechanism-based structural model for future analyses.

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D-08: *Sulav Duwal* A multiscale systems pharmacology framework to predict drug-class specific prophylactic efficacy of antivirals against HIV

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Objectives: Despite intense research, a complete cure and an effective vaccine against HIV have remained elusive till now. This emphasizes the importance of prevention strategies such as pre-exposure prophylaxis(PrEP) to curb the spread of HIV[1]. Currently, there are more than 30 antiretrovirals belonging to 4 major drug class for HIV-1 treatment and only two of them belonging to nucleoside reverse transcriptase inhibitor (NRTI) are approved for PrEP. The challenge is to rationally prioritize other antiretrovirals for PrEP repurposing and optimize the administration schemes. To this end, we extended the previously developed system pharmacology framework for NRTI for all antivirals and tailor-designed the hybrid deterministic-stochastic algorithm for efficient computation.

Methods: Previously, we built a multiscale modular systems pharmacology pipeline to assess the prophylactic efficacy of antivirals belonging to nucleotide reverse transcriptase inhibitors [2]. The pipeline meaningfully integrates processes of various scales. This includes modelling and simulation of the molecular mechanism of action at microscale level to meso-, macro- and population scale processes, such as the drug pharmacokinetics, viral replication dynamics, vertical viral transmission, up to the long-term infection probabilities after repeated virus exposure, akin to a clinical trial. In our recent works, we extended the pipeline for all antiviral classes considering their respective mode-of-action [3]. We utilized the branching process theory to derive drug-class specific concentration-prophylactic efficacy curve (dose-response curve).

Secondly, we employed a recently developed hybrid deterministic-stochastic algorithm based on Monte Carlo technique known as EXTRANDE [4]. EXTRANDE utilizes the thinning technique which allows exact simulation of a stochastic process (viral dynamics) embedded in a dynamically changing environment (antiviral pharmacokinetics). We extended EXTRANDE by introducing stopping criteria based on dynamically adapting extinction simplex derived from the branching process. This guarantees that the probability of falsely classifying a trajectory as an infection event is below a user-defined threshold, while the computational run-time is optimal for the user-defined threshold [3].

Results: In vitro measured drug potency (IC50, IC90) usually guides the design of PrEP trials [5]. We showed that such direct translation of in vitro drug potency to prophylactic efficacy is systematically misleading [3]. Except for reverse transcriptase inhibitor, the in vitro potency overestimates the prophylactic efficacy. Furthermore, we derived drug-class specific concentration-prophylactic efficacy curves which properly translates the in vitro measured drug potency to prophylactic efficacy. We observed that the shape of the concentration-prophylactic efficacy for co-receptor antagonists, reverse transcriptase inhibitors and integrase inhibitors is a classical Emax equation, whereas for protease inhibitors it is a power function.

Using the framework, we benchmarked all the treatment-approved antivirals and predicted that oral darunavir, efavirenz, nevirapine, etravirine and rilpivirine may provide complete protection at clinically relevant concentrations against wildtype virus [3]. Utilizing the population pharmacokinetics of dolutegravir, we assessed various prevention strategies based on dolutegravir. We predicted that the plasma concentrations of 145.18 and 722.23nM prevent 50- and 90% sexual transmissions respectively.

Conclusions: Herein presented systems pharmacology framework and algorithm can be used to select or rule-out PrEP candidates based on their prophylactic efficacies. Moreover, the algorithm allows for exact and efficient simulation of various administration strategies. This can be used to assess, design and optimize the administration strategies.

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D-09: *Vincent Madelain* Ebola viral dynamics in nonhuman primates: insights into virus immuno-pathogenesis and antiviral strategies

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Objectives:

The 2014-2016 Ebola virus outbreak in West Africa, with more than 11,000 deaths, showed that hemorrhagic fever viruses are posing an increasing threat to public health, and the need to develop effective antiviral approaches [1]. Our group and others have focused since 2015 on the assessment of polymerase inhibitor favipiravir, which has shown in vitro and in vivo efficacy against several viruses, including Ebola, Lassa and Marburg viruses [2–4]. Part of this evaluation, this work aimed to:
- Develop a mechanistic host pathogen model to characterize the role of innate, adaptive immune response and favipiravir treatment on Ebola pathogenesis in NHPs.
- Predict the effect of treatment efficacy and timing of initiation on survival in NHPs.

Methods:

1) A total of 44 cynomolgus macaques were infected with Ebola virus, including 16 that were treated with doses of favipiravir ranging from 100 to 180 mg/kg BID initiated two days before viral challenge [3,5]. Frequent measurements of viral load, cytokines levels, cytotoxic CD8 T cells and favipiravir plasma concentration were collected and integrated into mechanistic models of host pathogen interaction. Models of increasing complexity were fitted to these data to incorporate the effect of favipiravir on viral replication, the effect of innate response on controlling peak viremia and finally the adaptive immune response on viral clearance. At each stage, a systematic model selection was performed based on the value of the log likelihood of the viral load, and selected models were evaluated using VPC.
2) Next the viral dynamics model was extended to include time to death (joint model) [6]. A forward procedure was used to select the model variables included in the hazard function providing the best improvement of BIC. Model prediction was then validated externally using previously published data obtained with another potent polymerase inhibitor, GS-5734, in NHP to evaluate the model capability to capture the relationship between antiviral potency and survival times [7]. Finally, simulations studies were performed to extrapolate the impact of treatment potency and timing of treatment on viral load, immunopathogenesis and survival.
Model estimations were performed using the SAEM algorithm, implemented in Monolix software 2016R1.

Results:

1) Capture of the Ebola viral dynamics required to incorporate the effect of the innate response mediated by IFNα. The main role of IFNα was to increase the conversion of target cells into non permissive cells, and so to control the viral replication. Treatment with favipiravir, albeit modest, was sufficient to reduce viral replication and cytokine storm, while still conferring cell protection. After peak viremia, modeling identified that progressive increase in CD8 T lymphocytes expressing perforin shortened the half-life of infected cells from 3 days to 16 hours, allowing viral clearance in surviving animals. The EC50 of favipiravir was estimated

to 191 µg/mL, corresponding to an inhibition of 50% of the viral replication for the highest evaluated dose. 2) A joint model assuming that hazard rate was related to IFNα provided the best description of time to death. The model could reproduce both the viral load profiles obtained during treatment with GS-5734 and well predicted the survival rate of 100% observed in the experiment [7]. Using the model to further predict the efficacy of favipiravir and GS-5734 in various settings we predicted that: i) favipiravir initiation in post exposure up to D2 post challenge would maintain similar survival rate of about 60% compared to prophylaxis initiation, ii) treatments of higher potency could maintain 100% protection if administered before D4 and iii) treatment initiation after D5 would lead to 0% protection regardless of treatment efficacy.

Conclusions:

The model showed that mortality is primarily driven by the inflammatory reaction rather than by the virus replication per se. The early administration of a potent direct antiviral drug impairs viral replication, reduce the number of infected cells and consecutively the release of inflammatory cytokines. As the potency of the drug increases, the time window to initiate treatment after infection and save animals extends, but not over 6 days, when the cytokine storm can no longer be reversed. These results support the design of prophylaxis or post exposure trials for the evaluation of direct antiviral in future outbreaks.

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I-01: *Annika Schneider* Physiologically based pharmacokinetic modeling – application for renal and hepatic impairment

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Objectives: Hepatic and renal impairment can have an impact on pharmacokinetics in patients compared to individuals with normal hepatic or renal status. Currently, the regulatory acceptance of model-based assessments for such populations is still in discussion. The objective of the presented approach was to evaluate the potential and critical gaps of physiologically based pharmacokinetic (PBPK) modeling and its predictive power for an assessment of these disease states. Moreover, it was aimed to evaluate potential improvements. By use of adequately selected paradigm compounds, a path forward for this assessment was developed and is presented here.

Methods: In a stepwise approach, the current state of knowledge on physiological changes related to hepatic and renal impairment were compiled and integrated into a PBPK framework. Physiological changes considered in the PBPK framework were informed for blood flows, plasma protein concentrations, hematocrit, liver enzyme activities and glomerular filtration rate (GFR). By this, in-silico renal (mild/ moderate/ severe) and hepatic impairment (Child-Pugh A/B/C) populations were established and population simulations with several paradigm compounds were performed to test the compiled information for both diseases. All simulations were performed using the Open Systems Pharmacology Suite [1] and simulation results in the form of concentration-time profiles, maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) values were compared to respective clinical data obtained from literature [2-8]. As a qualification criterion for concentration-time profiles, a two-fold prediction range around the observed values was defined. Cmax and AUC values were evaluated using the geometric mean fold error (GMFE).

For hepatic impairment midazolam and alfentanil were chosen as paradigm compounds due to their nearly exclusive metabolism by CYP3A4. Amikacin was selected as a test case for renal impairment because of its nearly solely renal excretion. Midazolam pharmacokinetics was also examined for renal impairment to evaluate the influence of renal impairment on CYP3A4. In a next step the approach was applied to lidocaine and two subsequent metabolites to assess a more complex elimination scheme. For this purpose, a PBPK model for lidocaine and its metabolites was built.

Results: The PBPK approach was able to predict the mean pharmacokinetics of alfentanil, amikacin, and midazolam under renal and hepatic impairment well. 88% of all plasma concentration values were within a two-fold prediction range around the observed values. Cmax and AUC values were predicted with a GMFE of 1.698 and 1.351, respectively. The application to lidocaine and its metabolites also showed good agreement of available mean clinical data to the mean predictions with 74% of plasma concentration predictions lying within the two-fold prediction range. The GMFE of the Cmax and AUC values were 1.68 and 1.515, respectively. Nevertheless, the approach struggled with the prediction of the right variability within and between populations, especially for hepatic impairment populations. Further analysis of this limitation identified different underlying reasons, one of them being the limited translatability of the classification rules into physiological parameters, as well as the pathophysiological heterogeneity of populations with the same classification score.

Conclusions: The hereby presented approach was able to cover the rationale to predict the pharmacokinetics in renally and hepatically impaired populations based on healthy individuals. The current challenges towards a direct relation of categorization by Child-Pugh classes or apparent GFR values to physiological parameters were discussed, revealing key elements for further improvement. Additionally, a PBPK model for lidocaine and its metabolites was built which was well able to predict pharmacokinetics of these compounds in both patient populations.

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I-02: *Johannes Schropp* Characterization of bispecific antibodies and the ternary complex including an optimal dosing strategy

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Objectives: Bispecific monoclonal antibodies (BsMabs) are promising candidates in cancer immunotherapy. For example, BsMabs may simultaneously bind a T cell and a tumor cell. In general, a BsMab binds to two targets (e.g. receptors) forming two binary complexes. Both binary complexes further cross-bind with the same targets creating the ternary complex. Based on this binding kinetics, modeled by the law of mass action, several mathematical models [1]-[4] were developed to guide development of BsMabs. In this study, the level of occupancy of the ternary complex is considered as the produced effect of the BsMab drug, and the behaviour of the ternary complex in relation to the BsMabs concentration is investigated. We apply a BsMab model [5] that incorporates linear elimination, internalization of the complexes, and synthesis and degradation of the targets. We will demonstrate by explicit formulas and simulations that due to the underlying cross-binding the ternary complex has some special uncommon features such as (i) for escalating BsMab doses the level of occupancy of ternary complex decreases and finally vanishes, and (ii) the ternary complex is still fully available although the BsMab concentration is already below limit of quantification. Based on this behaviour a method to develop an optimal dosing strategy for a BsMab drug is presented.

Methods: To develop an optimal dosing strategy, a drug concentration-ternary complex load relationship is needed. First, Li et al. [3] revealed that the core of the dynamics in a similar full BsMab model is governed by the pure binding relations. This so-called equilibrium binding (EB) model describes the instantaneous answer of the binary and ternary complexes of the full BsMab model and its QE approximation for a constant offer of total drug concentration Ctot, and total targets RtotA and RtotB. We additionally present an explicit representation formula describing the level of occupancy for the ternary complex RCAB(C) with respect to the free drug concentration C. This representation proves that in contrast to classical concentration-effect terms, the level of occupancy for escalating doses decreases and finally vanishes. Second, following Li et al. [3] we visualize the level of occupancy of the ternary complex in a (Ctot(C), RCAB(C)) diagram. Diagrams of that type show an optimal level of occupancy for the ternary complex in the EB model, if the total amount of drug is within the range between the minimum and the maximum of RtotA and RtotB which defines the optimal working area of a BsMab. Due to our explicit representation formula, we reformulated this relation for the optimal working area in free drug concentration. Using parameter values based on literature, we show that the ternary complex is working at an optimal level of occupancy even if the level of the free drug is below the level of quantification. Third, the rapid binding assumption used in the QE approximation and singular perturbation theory [6] ensure that (i) the dynamics of the full BsMab model and its QE approximation are nearly identical, and (ii) the solutions of these models in the binary and ternary complexes move along the predictions of the EB model. This allows us to translate the EB results to the full model or QE approximation.

Results: We show that an optimal dosing strategy for the maximal level of the ternary complex occupancy has to generate a level of Ctot(t) which is between the maximum and the minimum of the total amount of targets A and B for as many time points as possible. This defines the optimal working area for the full model and its QE approximation. Within this framework optimal redosing points are points when the total amount of drug leaves the optimal working area via its lower bound and the next optimal dose has to lift the total

amount of drug from the lower to the upper limit of the optimal working area. Using this principle an optimal dosing schedule for the BsMaBs model can be established provided all model parameter values are known.

Conclusions: The relationship between BsMab concentration and level of ternary complex occupancy is described by cross-binding behaviour. Simulations from a full BsMab model showed that the ternary complex has some unique behaviour which has to be confirmed by experimental data. Finally, we present an optimal dosing strategy based on a free BsMab concentration – ternary complex relationship.

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I-03: *Pascal Schulthess* Frequency-domain derived optimisation of cell cycle specific cancer treatment

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Objectives: It was recently demonstrated that key biological control systems (such as the MAPK pathway) are highly sensitive to the frequency of external stimuli in a non-intuitive manner which cannot be predicted by conventional pharmacometrics approaches [1]. This suggests that quantitative systems pharmacology (QSP) can provide novel insights into optimal dosing regimens which could add a new dimension to the design of novel treatments. However, methods for such an approach are currently lacking. Recently, we illustrated the utility of frequency-domain response analysis (FdRA), a method widely used in electrical and control engineering, using several generic pharmacokinetic-pharmacodynamic case studies [2]. We now demonstrate the use of FdRA to optimise treatment regimen for cell cycle specific chemotherapy.

Methods: FdRA informs on the response of a QSP model to a wide range of perturbations as used in repetitive treatment regimen and enables the identification of treatment frequencies that amplify or attenuate the treatment response. Here, FdRA is applied to a cell cycle specific two compartmental model of tumour growth dynamics [3]. The proliferating cells in G1, S, G2, or M phase of the cell cycle inhabit the first compartment while quiescent cells in G0 phase reside in the second compartment. While the proliferating cells are degraded, growing and transfer to G0 phase, we assume that the quiescent cells are not degraded but only transfer back to become proliferative. The pharmacokinetic model of Etoposide (VP-16), a cell cycle specific anti-cancer drug widely used against childhood leukaemia, testicular tumours, Hodgkin's disease, large cell lymphomas and small cell lung cancer consists of two compartments. Etoposide in plasma stimulates the degradation of proliferating tumour cells. By assuming repetitive bolus doses at frequencies between two per day and one per ten days and while keeping the total dose administered over the course of treatment constant, we numerically measure the amplitude of the plasma concentration of Etoposide (as input) as well as the amplitudes of the total number of tumour cells at distinct times during treatment (as output). The output to input amplitude ratio is then plotted over the dosing frequency in a diagram similar to the Bode diagrams used in engineering [2].

Results: Comparing the amplitude ratios at different time points during treatment, we observed that the frequency response for all time points (30, 45, 60 days after treatment start) assumed a similar shape with a low amplitude ratio for less frequent and a high amplitude ratio for high frequent dosing. Lastly, the amplitude ratio of the 30 days' time point was larger than for all other time points for less frequent dosing while it was the smallest as compared to all other time points for high frequent dosing. An amplitude ratio intersection for the points at 59 doses per 100 days is observed. Thus, in order to decrease the fluctuations in tumour mass as well as total tumour mass high frequent low dose treatment is advised.

Conclusions: Drug dosing regimen can significantly impact drug effect and, thus, the success of treatments. Here, we show that FdRA, as a novel analytical method in systems pharmacology, facilitates not only the characterisation of QSP model dynamics with respect to the presence and magnitude of time-delays, model stability and performance but also aids the understanding of the pharmacological system and the optimisation of drug treatment regimen.

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I-04: *Bernard Sebastien* Hypoglycemic risk kinetics modeling as patient achieving glucose control in insulin-naïve T2DM patients initiating glargine 300U/mL versus glargine 100U/mL

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Objectives: The Edition 3 (NCT01676220)was a multicenter, randomized, open-label, two-arm parallel-group Phase 3 study comparing the safety of efficacy of glargine 300U/mL (Gla-300) versus glargine 100U/mL (Gla-100) once daily in insulin-naïve type 2 diabetes patients inadequately controlled on oral glucose-lowering drugs (1). A significant lower risk of hypoglycemia was found over the 6-month treatment period with Gla-300 versus Gla-100 while HbA1c levels decreased similarly with the two treatments. In an exploratory analysis, a modeling approach was applied to understand and compare the hypoglycemia risk kinetics between the two insulins when patients were titrating their insulin doses to achieve a protocol defined pre-breakfast plasma glucose level (f-SMPG).

Methods: Treatment emergent documented symptomatic hypoglycemia confirmed by blood glucose reading below 3 mmol/L (54 mg/dl)) was used in the analysis, where the threshold of 3 mmol/l was selected considering the glucose meters accuracy and ensuring the hypoglycemia alert value below 5.9 mmol/L (70 mg/dl). Time to first hypoglycemic event occurred within the 6 months of the study were modeled versus pre-breakfast self-monitored plasma glucose (f-SMPG) values as the time-varying covariate. F-SMPG was used since it was most frequently measured and almost daily during the dose titration period. It is more informative to track glycemic profile over time compared to other glucose measures in the study. A parametric time to event survival model with f-smpg at baseline, as time-varying and treatment (gla-300 and gla-100) as covariates was established with events assumed to follow a Weibull distribution. All hypoglycemia free patients were considered as censored at 6 months.

Results: There were 94 events overall in first 6 months in Edition 3 with 7.7% patients on gla-300 and 14.2% patients on gla-100 having at least 1 event. There was a statistically significant (p=0.001) trend for higher risk of hypoglycemic event associated with lower f-SMPG (2 treatments combined). A statistically significant (p= 0.002) treatment-by-time-varying f-SMPG interaction was also identified in the model indicating differential treatment effect of gla-300 compared to gla-100 during the insulin titration and f-SMPG reduction from the baseline phase. For gla-300, the global trend for decrease of risk over time is approximately compensated the hazard increase induced by the decrease in f-SMPG, leading to an estimated hypoglycemic hazard almost constant across time. For gla-100, the estimated hypoglycemic hazard is higher during the titration period, reduces and approaches plateaued at the later part of 6 month. Overall, the hypoglycemic risk is higher for patients on gla-100 than for patients on gla-300 during the titration phase. The beneficial effect of gla-300 is larger when time-varying fasting SMPG is higher (hazard decreased by 80% for f-SMPG=140 mg/dl as compared to hazard reduction of 36% for f-SMPG=100 mg/dl), which is during the titration phase of the study. A similar model was also obtained in Edition 2 (NCT01499095, 2), a similar Phase 3 study for prior insulin patients, for the first 6-month treatment period with a reduced magnitude in hypoglycemic risk benefit. The reduced hypoglycemic risk kinetics difference between gla-300 and gla-100 in Edition 2 could be due to the relatively lower f-SMPG in prior insulin patients at the beginning of the study.

Conclusions: The modeling approach, in particular the consideration of whole f-SMPG dynamics in the model, enabled to better characterize the kinetics of hypoglycaemic risk in patients receiving either of the two insulin glargine Gla-300 and Gla-100.

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I-05: *Malte Selch Larsen* Impact of trial designs, study conditions and statistical methods on the estimation of drug potency and power in clinical trials of haemophilia with inhibitors

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Objectives

Historically, clinical trials of haemophilia with inhibitors have been challenged by *i*) the small patient population, *ii*) event-type outcome and *iii*) potential placebo effect [1]. There is therefore a need to optimize the clinical trial designs and analysis methods in this therapeutic area.

The aim of this work was to evaluate the impact of different trial designs and study conditions on the estimated drug potency and to compare traditional statistical methods with repeated time-to-event (RTTE) modelling in terms of power of finding a statistical significant drug effect.

Methods

Baseline analysis of bleeding events

Baseline data on the occurrence of bleeding events (BE) in 23 haemophilia patients with inhibitors were obtained from a study by Ljung et al [2]. A RTTE model was developed to describe the probability of BE over time in haemophilia patients with inhibitors. Model selection was based on comparison of the objective function value, Kaplan-Meier visual predictive checks and precision of parameter estimates. The Laplace estimation method in NONMEM version 7.3 [3] was used.

Simulation model, trial designs and study conditions

The hypothetical drug ($drug_H$) was assumed to be given subcutaneously once a week and to display a two-compartment pharmacokinetic (PK) distribution with first-order absorption. The exposure-response relationship of $drug_H$ was described by an E_{max} model and a proportional placebo effect of 25 % [1] was implemented for the treatment period.

Four different trial designs, previously used in clinical trials of haemophilia [2, 4, 5], were evaluated: parallel-group design (PG-design), placebo-controlled parallel-group design (PGPLC-design), crossover design (XO-design) and placebo-controlled crossover design (XOPLC-design). Study conditions evaluated in this work included different sample sizes, study durations and doses.

Evaluation of precision and accuracy of the estimated drug potency

The stochastic simulation and estimation (SSE) method in PsN [6, 7] was used to evaluate the effect of different trial designs and study conditions on the precision and accuracy of the estimated EC_{50} of

$drug_H$ (1000 samples). The accuracy was evaluated based on the median, while precision was evaluated based on the width of the 95% confidence interval and the percentage of estimates with relative error ± 75%.

To illustrate the effect of an inaccurate estimate of EC_{50} on dose selection, the relationship between annualized bleeding rate (ABR) and dose of $drug_H$ were plotted for the true EC_{50} value and for EC_{50} estimates with ± 50 and 75% relative error, respectively. Assuming a treatment aim of 3 BE/year, the appropriate dose was derived for each EC_{50} estimate and the resulting ABR was compared to the treatment target.

Evaluation of power

The SSE method was used to estimate the relationship between sample size and the power to identify a significant treatment effect for RTTE modelling, *t*-test (two-sided) and negative binomial regression (p=0.05).

Results

The baseline hazard was accurately described by an exponential distribution with a hazard constant of 22.6 $year^{-1}$ and inter-individual variability of 77.3% coefficient of variation. All trial designs and study conditions provided accurate estimates of EC_{50}. However, the crossover designs displayed up to four-fold higher precision relative to the parallel-group trial. In general, the presence of a placebo-group did not increase the precision. However, a beneficial effect of the placebo-group was observed for the lower dose, probably reflecting the increased difficulty of separating the drug effect from the placebo effect when the drug effect is low.

To meet the assumed treatment target of 3 BE/year, a dose of 150 mg/kg would have been required given the true EC_{50}. In case of inaccurate estimates of EC_{50} e.g., relative error of -50 and -75%, doses of 75 and 37.5 mg/kg would have been selected resulting in ABRs of approximately 5 and 9 BE/year, respectively.

The crossover designs displayed up to three-fold higher power relative to the parallel-group designs. As for the traditional statistical methods, the *t*-test and negative binomial regression systemically displayed a lower power than RTTE modelling.

Conclusions

We found that utilization of crossover designs in combination with RTTE modelling can markedly reduce the required sample size and study duration, while ensuring high power and precise estimation of EC_{50}, in clinical trials of haemophilia with inhibitors.

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I-06: *Jérémy Seurat* Robust designs accounting for model uncertainty in longitudinal studies with binary outcomes

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Objectives:

Nonlinear mixed effect models (NLMEMs) are widely used for the analysis of longitudinal data obtained during clinical trials. An appropriate choice of design is crucial to get precise estimation of parameters and/or good power of tests, especially in the case of sparse sampling. For this purpose, optimal design based on the expected Fisher Information Matrix (FIM) can be used instead of clinical trial simulations (CTS). A method evaluating the FIM, without any linearization, based on Monte-Carlo and Hamiltonian Monte-Carlo (MC/HMC), was proposed [1] and implemented in the R package *MIXFIM*, which performs well with both continuous and discrete data. Nevertheless, this approach requires *a priori* knowledge of the model, which may lead to non-informative designs if the guessed model was inaccurate. We aimed to propose a new robust design approach based on MC/HMC to account for model uncertainty and to ensure a compromise between the overall precision of estimation and the power of the Wald test to detect a covariate effect. We illustrated and evaluated by CTS the proposed approach through an example of designing a longitudinal trial with binary outcomes.

Methods:

First, to find informative designs given one predefined model, different optimality criteria based on the FIM evaluated by MC/HMC were computed, according to different purposes: the D-optimality (*i.e.* maximizing the determinant of the FIM) to optimize the precision of the whole set of parameters, the D_S-optimality to accommodate situations in which only a subset of the parameters is of interest (*e.g.* covariate effects), and the DD_S-optimality to find a compromise between the D- and D_S-optimality [2]. Then, to account for model uncertainty in design optimization, we assumed a set of predefined candidate models with their respective weights and we computed robust designs across these models using compound CD-, CD_S- and CDD_S-optimality [3,4].

These methods were applied to design a study with two treatment groups, using a logistic model for repeated binary responses which correspond, for example, to a decrease of 11.1 points of the UDysRS Part III Impairment scale in Parkinson disease [5]. Four candidate models describing the evolution of the logit-probability of the response over time, from 0 to 12 months, were defined: M1 linear, M2 log-linear, M3 quadratic and M4 exponential models. Assuming the first and the last time fixed to 0 and 12 respectively, we performed combinatorial optimization of 2 among 11 times, between 1 to 11, to obtain different four-samplings protocols which were optimal for each model separately or optimal over the four models. Using the expected FIM, we also predicted the average power to detect a significant treatment effect over the four models, with different optimized protocols, *vs.* a non-optimized equi-spaced protocol $\xi_{ES} = (0,4,8,12)$.

CTS were then used to evaluate the performances of the CDD_S–optimal design (ξ_{CDDS}) *vs.* the DD_S-optimal design for a given model M_k (ξ_{DDSk}) *vs.* the equi-spaced design (ξ_{ES}) in terms of bias and imprecision of estimates. For that we simulated 500 datasets under each model and analyzed them using SAEM algorithm in MONOLIX 2016R1 [6]. The relative standard errors and power of test observed from CTS were also compared to those predicted using the expected FIM.

Results:

The robust optimal design was different than the one optimized for each model, *e.g* ξ_{CDDS} = (0,4,11,12) across four models *vs.* ξ_{DDS1} = (0,2,11,12) for M1. Misspecification of models led to designs with D-efficiencies as low as 64.6%. The compound criteria provide robust CD-, CD_S- and CDD_S-optimal designs which are efficient across the four candidate models, with D-efficiencies always above 80%. With the designs ξ_{ES}, ξ_{DDS1}, and ξ_{CDDS}, we predicted respectively 358, 320 and 274 subjects needed to achieve an average power of 90% to detect the treatment effect over the four models. The simulation study confirmed that, for the same number of subjects, the robust design ξ_{CDDS} is more informative and performed better than ξ_{DDS1} and ξ_{ES}. This design gave acceptable estimation errors and good power, closed to those predicted using the expected FIM.

Conclusions:

The proposed design strategy based on MC/HMC and compound optimality theory, is a relevant approach which can be used to efficiently design longitudinal studies. This approach accounts for model uncertainty and ensures a balance between the overall precision of estimation and the power of the Wald test to detect a covariate effect.

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I-07: *Shringi Sharma* A Joint Model to Evaluate the Relationship between Lymph Node Response and Progression-Free Survival in Chronic Lymphocytic Leukemia

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Objectives: In oncology drug development, tumor growth related metrics (such as, tumor size ratio or time to tumor growth) are being increasingly used to predict clinical outcomes such as progression free survival (PFS) and overall survival[1]. Modeling was conducted to simultaneously characterise the longitudinal tumor (i.e. lymph node, LN) growth and PFS in subjects with relapsed/refractory chronic lymphocytic leukemia (CLL). The ability of the model to predict PFS (i.e. simulate PFS distributions) was evaluated.

Methods: A phase 3 placebo-controlled study which included 207 subjects treated with idelalisib (IDELA) in combination with bendamustine (B) and rituximab (R), and 208 subjects treated with B/R was included in the analysis. The final dataset included 1337 tumor measurements from IDELA +B/R and 1053 measurements from B/R treatment arms (measured at baseline and Weeks 12, 24, 36 and 48).

Longitudinal LN data was analysed using a tumor growth inhibition (TGI) model[2], as shown below:

$$y_i(t_{ij}) = y_{0,i} \cdot \exp[KL_i \cdot t_{ij} - KD_i/\lambda_i \cdot (1-e^{-\lambda_i \cdot t_{ij}})] + eps_{ij}$$

where y is the LN size; KL and KD are the LN growth rate and LN growth inhibition rate, respectively; λ is the rate constant that accounts for a decrease in LN growth inhibition rate (KD) over time (t); y_0 is the LN size at baseline (BSLN); j is the observation of an individual i.

PFS was described using a single time-to-event model with the hazard (h) defined as a function of longitudinal LN growth, as shown below:

$$h(t) = \lambda \bullet \exp[\beta * \log(t)] \bullet e^{yhaz \bullet y(t)}]$$

where, β is the baseline hazard, λ is the shape parameter for Weibull distribution, and yhaz is the estimated link between model predicted LN size at time t, y(t), and the hazard. The estimation of LN size and PFS parameters was conducted simultaneously, which allows estimation of model parameters from a joint likelihood that combines uncertainty in parameter estimates. A non-linear mixed method approach implemented in NONMEM 7.4.0 was used, assuming lognormal inter-individual variability and an additive residual error. Simulations (N=1000) were conducted, based on the final model, to predict the PFS distributions and compare with observed data.

Results: Longitudinal LN growth was well characterized by the TGI model with inter-individual variability estimated on all parameters; mean (%CV) values were y_0=5220 mm^2 (65), KL = 0.03 $month^{-1}$ (151), KD = 0.64 $month^{-1}$ (35), and λ = 0.24 $month^{-1}$ (43). Larger BSLN size was associated with a greater tumor growth inhibition rate (KD); ~±30% change in KD at the 5^{th} and 95^{th} %ile of BSLN, relative to median BSLN values. The parameter estimates for the PFS model were β=0.0017 $month^{-1}$, λ=1.2 and y_{haz}= 6.8e-05 mm^{-1}. Based on the predicted Kaplan-Meier distributions, the joint model showed good performance in predicting PFS.

Conclusions: The LN growth dynamics and the observed PFS were well characterized by the joint model in subjects with CLL. By linking the full time course of LN growth as a predictor of PFS in a parametric time to

event model, the present model was successful in predicting PFS. This model based framework could be leveraged for predicting clinical outcomes when performing clinical trial simulations to support clinical study designs or alternative dosing regimens.

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I-08: *Dmitrii Shchelokov* A semi-mechanistic model of targeted therapy for melanoma

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Introduction: Targeted therapy with BRAF inhibitors has resulted in significant progress in the treatment of metastatic melanoma bearing BRAF V600E mutation. Since 2011 FDA had approved a series of targeted inhibitors of MAPK pathway, the first of them was BRAF inhibitor vemurafenib [1]. Despite the initial success of clinical outcomes, most patients ultimately develop drug resistance and relapse. The recent studies evidence that HGF/c-MET pathway plays a crucial role in the development of drug resistance mediated by tumor microenvironment [2]. Implementation of these experimental findings could help to develop a more realistic model of targeted therapy for melanoma and to evaluate the potential role of c-MET inhibitors in melanoma treatment.

Objectives:
• To develop a semi-mechanistic model of targeted therapy for melanoma (using vemurafenib as an example) which is able to describe the emergence of drug resistance during therapy
• To describe inter-patient variability in response to vemurafenib treatment
• To explore the effect of c-MET inhibitors in combination with BRAF inhibitor vemurafenib for different types of virtual patients

Methods: The model comprises of 6 ordinary differential equations (ODEs): 4 of them describe cellular dynamics and other 2 describe pharmacokinetics (PK) of the drug. PK model and parameters for vemurafenib were taken from FDA clinical pharmacology and biopharmaceutics review [3]. The cellular block of the model includes 4 various cell states (c-MET negative/positive and sensitive/resistant to BRAF inhibitor melanoma cells, respectively) and describes proliferation, apoptosis, and transition between cell states, as well as effects of vemurafenib and HGF on the rate of proliferation. An effect of c-MET inhibitors was simulated by decreasing parameter Emax of HGF stimulatory effect on proliferation of c-MET positive cells. Tumor volume was defined as an explicit function of a total number of melanoma cells and used to measure change from baseline during the therapy.

To introduce an inter-patient variability in the model for further multiple simulations we compiled available published data and tried to estimate variability for several numbers of parameters. Also, we tried to estimate the amount of pre-existing drug-resistant cells in the tumor on the basis of clinical data on time to progression. It is important to note due to the lack of data we are able only to assume the probability distribution of each parameter and approximately to estimate mean and variance. The R package ‘stats’ were used for random generation of parameters sets according to their function of distribution (R v3.2.1) [4].

Results: Developed model qualitatively reproduces all types of tumor response to vemurafenib monotherapy according to RECIST criteria: complete response, partial response, stable disease and progressive disease. To evaluate the predictive ability of the model in a quantitative manner we compared results of multiple simulations with clinical outcomes. An overall response rate was 70% versus 53% (95% CI, 44 to 62) observed in phase 2 clinical trial [5]. The model tends to overestimate the treatment effect possibly due to we did not take into account an intermittent administration and dose reduction in case of adverse events. The subsequent analysis of the multiple simulations revealed a correlation between maximal response and parameter Emax of HGF effect which depends on c-MET expression level. This

observation is supported by experimental data which shows that HGF rescue strongly correlates with c-MET expression by melanoma cells [6]. The model predicts that usage of c-MET inhibitors in combination with BRAF inhibitors could improve on response and overall response rate, as well as delay or avoid BRAF-inhibitors resistance development and relapse.

Conclusion: The present work focused on the development of a semi-mechanistic model of targeted therapy for melanoma which is able to adequately describe clinical data and drug resistance development. Obtained results are consistent with recent experimental observations and confirm the hypothesis about the role of HGF/c-MET pathway in the development of resistance to BRAF-inhibitors. To conclude our results show a potential perspective of BRAF/c-MET inhibitors combination therapy for melanoma to improve overall response rate and overcome drug resistance.

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I-09: *Yucheng Sheng* Item response theory modelling of motor scores to investigate feasibility of reducing proof-of-concept trial for Parkinson's disease

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Objectives: Parkinson's disease (PD) is a progressive condition. The total score of Part III (Motor Examination), a composite of 33 categorical items of MDS-UPDRS (Movement Disorder Society United Parkinson's Disease Rating Scale), is a commonly used efficacy endpoint in clinical trials of anti-PD drugs. It is conceivable that among the 33 items some are more informative than others. In this work, we seek the most informative items in MDS-UPDRS Part III, using Item Response Theory (IRT) modeling analysis, and compare the power for a proof-of-concept study between IRT and conventional methods by simulation.

Methods: We developed a longitudinal IRT model to describe motor examinations of MDS-UPDRS using the Parkinson's Progression Markers Initiative (PPMI) data set which contains 5 years observations. All motor items from MDS-UPDRS were linked to one latent variable representing "Severity" via probability functions. The score change over time for each item then reflected the longitudinal change in this variable. We assessed the relative informativeness of individual items. Following IRT model validation, trial simulation was conducted to assess PD progression, when using the sum of all 33 item scores or of the most informative ones. Item scores were back-transformed from the IRT model with different, presumed treatment effects. Probability of success (or Assurance) was estimated from drug effects which that were hypothesized to follow a uniform distribution of between 0.1 and 0.5. The ability to detect treatment effects was compared for the sum of item scores and for the "Severity" variable.

Results: Two-parameter logit item response model was used to link the probability of each item score to the latent "Severity". "Severity" change over time was described by a linear model, and "Severity" at baseline was the only influential covariate on the slope. Inter-occasion variability was also added to "Severity". Longitudinal "Severity" change reflect well the item score change over time. Visual predictive check for total scores, which were summed up from back-transformed item score, also suggested the final IRT longitudinal model sufficiently captured the density and changes of total scores. Seven items from left body side – hand movement, finger tapping, pronation-supination, toe tapping, leg agility and rigidity of lower and upper extremity – were identified as the most informative items from all 33 items. The IRT analysis demonstrated a higher power to detect drug effects than the total-score-based analysis, either with all items or with the selected items. Assurance analysis suggested that 300 subjects per arm in a 2-year trial reached more than 70% probability of success from the IRT method with the selected items, whereas that from the conventional method of total score was less than 65%.

Conclusions: The IRT modelling analysis provides higher power to detect drug effects and results in smaller sample size for a proof-of-concept study. For the IRT method, the power was greater when all items were included, while for the conventional total score method the power was greater when only the most informative items were included. Simulations from this IRT model showed the "probability of success" to evaluate design options and promised for more efficient proof-of-concept studies in PD patients.

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I-10: *Christian Siebel* Consensus on doxorubicin dosing in infants and children: pharmacokinetic simulations and Delphi process

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Objectives: Despite their cumulative dose-dependent cardiotoxicity anthracyclines, such as doxorubicin, are still a mainstay for the treatment of both adult and paediatric cancer. However, dose recommendations especially in young patients have been developed more empirically rather than being based on pharmacological data. Large differences exist in doxorubicin dose and infusion time between paediatric treatment protocols and dose reduction strategies for infants vary largely between the different protocols. In a selection of treatment protocols that were evaluated in this study doxorubicin dose range was 15 – 50 mg/m² and infusion time varied from 15 min to 48 h. As the prevention of chronic cardiac side effects receives more attention with the growing number of childhood cancer survivors, we ask how population pharmacokinetic (PK) simulations in combination with a Delphi approach could aid in developing more rational dosing strategies for doxorubicin in paediatric patients.

Methods: A model-informed process was developed based on an already published population PK model for doxorubicin (described in [1]). In brief, pharmacokinetic data from 94 paediatric cancer patients (aged 0.2 – 17.7 years) from the EPOC-MS-001-Doxo trial (EudraCT-Nr: 2009-011454-17) were evaluated to develop the model. According to this model doxorubicin clearance was linearly scaled to BSA with an additional power function of age on clearance. Based on the model Monte Carlo simulations were performed using NONMEM version 7.3 [2] to visualize the influence of differences in patient age and body composition on therapy intensity represented by AUC and c_{max}. Particular attention was drawn to the influence of various dose reduction strategies in infants and very young children. Further, alternative dose reduction strategies were developed that should allow achieving distinct AUC and c_{max} goals. For simulations generic children according to WHO and CDC growth charts were used and model parameters were fixed to the published final parameter estimates. Based on the simulation results a three-round Delphi approach was initiated. In this Delphi approach 28 expert clinicians (EPOC partners and selected clinical trial leaders) were asked to provide their opinion on

1. the goals of doxorubicin dose reductions within single protocols and
2. common PK targets between different protocols that might guide the administration of doxorubicin.

As background information the participants of the Delphi process were provided with the simulation results.

Results: Considerable differences in individual therapy intensity have been observed within currently applied paediatric treatment protocols. When taking the CWS-2002/CWSSoTiSaR protocol (dose: 20 mg/m², dose reduction in children < 1 year or weighing < 10 kg; infusion time: 3 h) as an example, AUC and c_{max} values are lowest in neonates (AUC = 507 µg*h/L, c_{max} = 57 µg/L), increase towards a maximum in children slightly above one year of age (AUC = 1002 µg*h/L, c_{max} = 138 µg/L) and then steadily declines in older children. The simulations further suggest that by adjusting the doxorubicin dose to age and BSA the individual therapy intensity can be tailored towards specific goals. Of note, AUC and c_{max} values are subject

to a substantial amount of inter-patient variability which needs to be taken into account when developing standardized dose reduction strategies that are based upon previously specified AUC and c_{max} goals. The first round of the Delphi process was completed by 8 of the 28 panellists, the second round was completed by 8 of the 28 panel members. Evaluation for consensus is still ongoing in a third round of the process.

Conclusions: Adjusting the doxorubicin dose to achieve defined therapy intensity goals in infants and young children may help to reduce the risk of chronic cardiac side effects while maintaining tumour efficacy. A simulation process in combination with a Delphi approach was conducted to establish a consensus for doxorubicin dosing rules in paediatric patients. Consented dosing rules need to be prospectively validated in a clinical trial.

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I-11: *Alena Simalatsar* Personalised delivery rate computation for intravenously administered anesthetic using Kalman filter

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Objectives: The controlled delivery of intravenous (IV) anesthetic, such as *propofol,* aims at fast and safe achievement and maintenance of a suitable depth of hypnosis, by ensuring appropriate effect site (i.e. brain) exposure to the drug. Today, such drugs are regularly injected by Target Controlled Infusion (TCI) systems, piloted by an open-loop algorithm based on Pharmacokinetic (PK) models. However, clinical conditions may markedly alter *propofol* pharmacokinetics and actual concentrations could significantly differ from predicted ones, leading to important under- or over-exposure. The situation could be improved by closing the loop with sensors providing regular real measurements of the anesthetic concentration in body fluids. The aim of the present study was to develop a closed-loop algorithm based on the classic open-loop algorithm presented by Shafer *et al* [1] combined with a Kalman filter using real-time plasma measurements. We also perform stability analysis of this algorithm by accounting for realistic measurement noise, periods and delays.

Methods: Kalman filter is used to estimate the personalized plasma drug concentrations. The algorithm first uses the population PK model to produce a vector *X'* of a priori estimates of the current concentrations in each compartment, with x'_1 representing the plasma. Then it computes the estimate covariance *P* defining the model inaccuracy that we associate with the inter-patient variability of Eleveld *et al* [2]. Once a new measurement *y* is available, the measure residual $d=x'_1-y$ is computed. Kalman gain *K,* accounting for both model inaccuracy and measurement noise, is updated to compute a posteriori vector of concentrations $X=X'+Kd$. The estimate of K is updated with every new measurement. In turn, vector *X* is updated every second using the latest values of *d* and *K* to be used by Shafer's [1] algorithm for continuous infusion rate adjustment.

A set of 1000 individual female patients (*70 kg, 170 cm, 36 y*) generated by the Eleveld *et al* model with inter-patient variability [2] and a fixed target concentration at *6 mg/L* during *60 mins* of surgical operation were chosen. To validate the algorithm the measurements for each individual were simulated with the corresponding inter-patient variability and two different intra-individual variability values (Eleveld *et al 47%* and twice smaller 23%) under the computed *propofol* infusion rate. The effect site Concentration-Time (CT) profiles for all individuals if they were administered the drug with the delivery rate computed using open-loop algorithm of classic TCI (U_{av}) and our algorithm (U_{ind}) were computed. The 95% prediction intervals (PI95%) for the two different intra-individual variability values, various measurements periods (1, 5, 10, 15, and 30 sec) and delays between the time stamp of the blood sample and moment when it is available for processing (0, and 30 sec) were computed.

Results: The PI95% for individuals being administered with U_{av}, obviously, did not depend on measurement noise, period or delay. It remained constant in all experiments and exceeded the 40% accuracy area. In turn, the CT profiles of selected individuals administered with U_{ind} computed assuming the *1 sec* measurement period remained within 10% of accuracy area, thus insuring four times more precise effect site exposures. With the increase of measurement period PI95% was becoming larger and already exited the 20% accuracy area, however, still remaining within the 30% one with *30 sec* measurement period. The

measurement delay had a smaller effect on algorithm stability than the period and played a role only before the steady-state was reached.

The scenario with period of *15 sec* and delay of *30 sec* was considered as a realistic one. When assuming the maximum measurement noise the PI95% for individuals being administered with U_{ind} had a tendency to be border line between 20% and 30%. The PI95% decreased lowering measurement noise such that the PI95% of virtual individuals administered with U_{ind} stayed within the 20% accuracy area resulting in effect site CT profile variability being more than twice smaller than if they were administered with U_{av}.

Conclusions: We show that the approach based on Kalman filter ensures more precise and thus safer plasma and effect site exposures than currently achieved with open-loop TCI pumps. Reducing the measurement periods may provide up to four times better accuracy for effect site exposure.

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I-12: *Erik Sjögren* Bridging physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) analyses in paediatric drug development: A case study based on intravenous esomeprazole

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Objectives: Model-based approaches are implemented in obligatory steps of pediatric drug development. Physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) are two modelling methods often proposed to characterize paediatric pharmacokinetic (PK) and to support clinical trial design in children [1]. The aims of this study were to adopt the two well established modelling and simulation (M&S) techniques, PBPK and PopPK, for scaling the PK characteristics of esomeprazole to a paediatric population and to establish complementary and synergistic modelling approaches for the selection of an optimal dosing regimen in children.

Methods: PBPK and PopPK models were built using PK-Sim [2] and NONMEM [3], respectively. Adult models were firstly developed [4] and then verified towards adult clinical data [5]. Paediatric models were refined and extrapolated from the verified adult models with systemic ontogeny for the PBPK method and allometric scaling for the PopPK method [6]. The children models were used to simulate approved dosage schedules in children [7] and predict area under the plasma concentration-time curve extrapolated to infinity (AUCinf). Exposure-matching analysis for paediatric dose selection was used [8], where the target was to match the AUCinf in adults (2.67 umol•h/L). Dose optimizations to the targeted AUCinf were carried out with both PBPK and PopPK paediatric models [9]. Determinations of weight-based cutoff regimens were performed in NONMEM with PBPK and PopPK based approaches and various numbers of weight cutoff.

Results: The PBPK and the PopPK adult models provided adequate descriptions of the esomeprazole's PK characteristics in adults. The predicted outcomes of the paediatric models were similar for children > 1 year. Some difference was observed for children < 1 year probably due to that maturation of metabolic activity was not accounted for in the PopPK paediatric model. With the approved dosing regimen both paediatric models predicted higher plasma exposure in children than reported for adults after a 20 mg dose. Consequently, the optimal doses were estimated to be lower than the approved doses. The deviation from the target AUCinf decreased dramatically when using optimal dosing regimens compared to the labelled dose. Even though additional body weight dose switches did not result in a meaningful improvement of the exposure matching, the between subject variability decreased for dosing regimens with one body weight based dose switch.

Conclusions: This study demonstrates how dose-optimization algorithms can be applied to both PopPK and PBPK derived models. In line with regulatory recommendations these complementary results can be used as support in selection of dosing regimen in children.

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I-13: *Mike K Smith* Implementing "best practice" in Pop PK modeling

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Objectives:

Capturing best practices, communicating and sharing these is a first step on the path to industrialising population modelling and increasing efficiency within organisations. Recent manuscripts [1-5] have disseminated "best practice" around various aspects of modelling, model diagnostics and reporting. These are invaluable for the new modeller, and useful for the experienced modeller in calibrating their work against expectations from the community, academia and from regulatory agencies. But few of these discussions of ***what*** is expected describe ***how*** this should be achieved [4, 5]. After all, each analyst will have their own preferred tools and even when analysts use a common tool, their experience and depth of knowledge in that tool may bring heterogeneity in how they implement even standard models and workflows. Providing "standardised" code, code snippets and templates for commonly used population modelling tasks allows analysts to focus on the pharmacology and statistics of a problem and less on the computer science and coding. We present how Pfizer are attempting to harmonise Pop PK modelling within our organisation, implementing the "best practices" expressed in our guidance into code that analysts can use as a skeleton for refining according to their needs.

Methods:

By using the R package `bookdown` we are able to incorporate the advice from the guidance alongside reproducible code and code snippets that illustrate how to implement the guidance. We can easily keep the "book" up to date, refining code that becomes out of date or where a better solution emerges, and extending the book by adding chapters on new topics as required. Code and output can be fully explained and annotated in the text, and output from the code is kept alongside so that the analysts can see both inputs and outputs from each step. Snippets of code can be presented that allow the analysts to pick and choose the code that applies to their situation. Topics covered include exploratory data analysis using the `tidyverse` R packages, structural model building for Pop PK models in NONMEM, model diagnostics using the R package `xpose`, covariate model building using PsN FREM and SCM implementations, model qualification using PsN routines and creating run record and parameter tables ready for reporting. The book can be compiled to GitBook (HTML), PDF or EPUB formats.

Results:

Example datasets and model code are presented to provide working examples. Example code is presented within the book and is executed at the time of compilation which ensures reproducibility. Current best practice methods using NONMEM, R and PsN are presented. The material covered aims to support the analyst in going from data checkout and exploratory data analysis to a qualified model ready for inference, and to provide standardised code for implementing the steps along that path. The book has been shared within Pfizer and analysts are providing feedback on the content and methods presented.

Conclusions:

While the standardisation of tools and coding practices within a company help efficiency in delivering model informed decision making, sharing these practices more widely would help refine the code and truly standardise these simpler aspects of Pop PK workflow, forming the basis of training material, and allowing analysts to focus on science rather than coding.

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I-14: *Tom Snowden* A comparison of two model reduction methodologies for a QSP bone biology system with denosumab dosing.

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Introduction:
The increasing use of quantitative systems pharmacology (QSP) and physiologically-based pharmacokinetic (PBPK) modelling in drug development has caused modellers to more commonly confront the issue of model complexity. Due to complexity, such mechanistic models are often difficult to work with , challenging to analyse, and generally not suitable for estimation purposes due to the large number of states and parameters to be handled - even if all unidentifiable parameters were fixed. Methods of model reduction [1], commonly applied in other fields of modelling, can provide a rational framework for addressing issues of complexity and yielding practical, reduced models that retain a high degree of predictive power and a mechanistic basis.

Objectives:
To compare and contrast two recently published methodologies of model reduction via application to an example QSP type model of bone biology. The first such methodology [2] uses inductive linearization and subsequent lumping of the system to obtain a reduced description, the second [3] employs lumping and empirical balanced truncation under the Petrov-Galerkin projection to achieve a reduction. Both methods are compared by being used for the reduction of a QSP type model of bone biology that can describe the effect of denosumab on bone remodelling and osteoclast/osteoblast numbers [4].

Methods:
The bone biology model [4] was implemented and validated in Matlab R2017b as an interacting system of 28 ordinary differential equations (ODEs). Through simulation and analysis, agreement between our implementation and the original publication was attained. Both methods of reduction were then applied to this implementation. The first methodology employs inductive linearization of the original model to produce a time-varying linear system [5], this linear system is then reduced via proper lumping. The second methodology operates entirely on the nonlinear system via the Petrov-Galerkin projection; lumping is employed until the stiffness coefficient is sufficiently reduced to enable the follow-up application of empirical balanced truncation. The resulting models were then compared in terms of accuracy and ease of use with respect to the original system. The primary metric of accuracy was taken to be the maximal relative error between the outputs of the original and reduced models at the various levels of reduction.

Results:
Both methods of model reduction were able to produce significantly simplified systems whilst retaining a high degree of accuracy. A highly accurate reduction from 28 to 8 state-variables was achievable under both methodologies. Notably, however, the lumping and empirical balanced truncation approach was able to yield a 21% lower reduction error at the 7-dimensional reduction, as compared with the linearization and lumping approach. Additionally, whilst the linearization approach is somewhat mathematically simpler and easier to implement, the necessary creation of a time-varying linearization matrix does somewhat obscure the meaning of the reduced model and detract from its mechanistic basis.

Conclusion:
Methods of model reduction can simplify complex systems and enable their more practical application in

the context of drug development. When comparing two such methods, we were able to demonstrate that an approach of lumping and empirical balanced truncation was able to produce improved results as over a linearization and lumping methodology when comparing the overall approximation error incurred and the properties of the reduced model.

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I-15: *Victor Sokolov* Evaluation of the utility and efficiency of MATLAB and R-based packages for the development of quantitative systems pharmacology models

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Objectives: Quantitative systems pharmacology (QSP) modeling is an integrative methodology used in support of drug efficacy and safety problems in pharmaceutical R&D [1]. The growing need for QSP modeling in the industry and in communications with regulators necessitates a more standardized, transparent and seamless workflow within a model development and testing environment [2]. We selected five packages designed in MATLAB and R, to evaluate their utility and efficiency through comparison of the corresponding workflows, which were tested across three semi-mechanistic QSP models.

Methods: We evaluated the performance and model development capabilities of five packages: the MATLAB-based IQM toolbox [3], mrgsolve [4], RxODE [5], the AZR ODE solver with a set of MSDr functions [6], and the IQR package [7], all five packages running in R. Each package was tested over three different QSP models: a model describing lipoprotein metabolism and PCSK9-targeting therapies (PCSK9 model: 17 ODEs, 47 parameters) [8], a model of renal glucose reabsorption (SGLT model: 23 ODEs, 45 parameters) [9], and a GLP1-stimulated food retention model (FR model: 11 ODEs, 25 parameters) [10]. All three models were developed using study-level data, with substantial mechanistic details and non-linear features. The QSP modeling workflow was executed step-by-step, for each package and each model, testing solver speed (for numerical solution of the ODE system), quality of visualization, parameter estimation algorithms, model diagnostic options, and compatibility with companion workflows of pharmacometrics.

Results: The IQM, AZR/MSDr and IQR use a highly flexible syntax, and handle standardized '.csv' datasets as inputs, thereby allowing the user to translate models and data from one package to another with minimal efforts, and regardless of the software environment (R or MATLAB). These modeling tools feature integrated parameter estimation tools, use a script-based workflow complemented with a user-friendly graphical user interface (GUI), and provide easy reproducibility and access to data exploration, parameter estimation and model simulation tasks.
RxODE and mrgsolve have proven to be powerful tools for simulations of population and QSP models with varying degrees of complexity and design. For both of these packages, the model structure is described in R code, and both packages may receive input from standardized datasets. mrgsolve is compatible with parameter estimation packages such as nlme, and nlmixr is used as the parameter estimation tool for RxODE-based simulations.
Solving of an ODE system with 20,000 time steps, for a single administration of a drug, was successfully performed in IQM, AZR/MSDr, IQR, mrgsolve and RxODE using the three QSP models. The RxODE was more than 10 times faster, in terms of solver speed, as compared to the other four. However, lag times could not be incorporated in RxODE-type models, and only mrgsolve and IQR were able to incorporate regression parameters from the datasets.
A parameter estimation procedure was carried out for 10, 5 and 7 parameters, based on study-level datasets with 876, 304 and 190 data points for the PCSK9, SGLT and FR models in IQM, IQR, AZR/MSDr and RxODE (nlmixr). AZR/MSDr, RxODE and IQM single-subject fitting was not stable compared to IQR. In addition to parameter estimation, the IQR package calculated the gradient and the Hessian of the objective function, providing 95% CI for fitted parameters and making the procedure very fast.

IQM, AZR/MSDr and IQR automatically provide common model diagnostics, *e.g.*, Observed *vs*. Predicted, Residuals and Time profiles plots. In addition, AZR/MSDr and IQM provide sensitivity analyses, with a host of graphical features for longitudinal data or tornado plots for single timepoint.

Conclusion: We compared QSP workflows in IQM, AZR/MSDr, IQR, mrgsolve and RxODE packages using three QSP models. All packages can handle identical model structures and dataset files, as well as a script-based workflow. While the RxODE ODE solver was the fastest among five packages. IQR and mrgsolve are the only two packages which can operate with regression parameters, and IQR is the only package to provide a parameter estimation tool that is fast and robust, with an estimation of parameters with 95% CI. The IQM, AZR/MSDr and IQR packages provide rich model testing toolkits and various goodness-of-fit metrics for QSP modeling, with AZR/MSDr having superior quality of visual outputs.

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I-16: *Eunjung Song* Bayesian estimation of parameters in the pharmacokinetic model

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Objectives: The pharmacokinetic (PK) estimation and dose individualization are important to obtain a favorable outcome in a clinical setting. The consultation of therapeutic drug monitoring (TDM) is especially based on only peak or trough concentrations. In this limited observation, the dose optimization for TDM can be determined using Bayesian inference, which include the pre-defined PK model with covariate-parameter relationships defined a priori. Therefore, the objective of this study was to develop a TDM package in Stan version 2.14 (Stan Development Team) with the R package Rstan (Stan Development Team).

Methods: The vancomycin, known as a typical two-compartment PK model, was selected for the example of Bayesian estimation, because the vancomycin is widely used for the practice of TDM. The trough concentrations were randomly generated in the virtual PK model based on literature PK parameters of vancomycin. Log Gaussian Priors for the PK parameters were applied, and Bayesian inference was conducted using Markov chain Monte Carlo (MCMC) simulation.

Results: In the current study, the PK parameters for the population model were estimated and then individual drug concentrations were predicted by the developed package. The package provided suitable estimates for the population model and its prediction performance was also comparable with the other alternative packages (Abott PKS system, *tdm*, etc).

Conclusions: This study developed an alternative TDM package based on RStan, which can be comparable predictability to the previous software packages such as the Abott PKS system. We expect that this result will provide an accurate estimation of the PK parameters and prediction of dose concentrations, unlike other competitors with the fixed parameters for the population PK model.

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I-17: *Felix Stader* A population database for elderly to inform physiologically-based pharmacokinetic models considering anatomical, physiological and biological system parameters

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Objectives: The aim of this work was to develop and verify a population database for people above the age of 65 years with necessary system parameters to inform physiologically-based pharmacokinetic (PBPK) models.

Methods: A structured literature search was performed to screen for age-dependency of anatomical, physiological and biological parameters required to inform a PBPK model. Included parameters were body height, body weight, organ weights, cardiac output, regional blood flows, plasma binding protein concentration and glomerular filtration rate. Abstracts were screened, and studies included if the study population was Caucasian (being defined broadly and included Europeans, North Americans and Australians), at least age was reported in addition to the parameter of interest, and individuals were healthy, or the disease was deemed unlikely to affect parameters of interest. Data were separated into a development and verification dataset. Studies in the development dataset had to report sex, body height, body weight, ethnicity and location of the study in addition to age as necessary covariates to be able to describe correlations between system parameters. Otherwise, studies with less reported covariates were used in the verification dataset. Age-dependency could be estimated if at least three different studies reported the parameter of interest with one value in each age decade. Otherwise, age-dependent effects could not be investigated, and similar values were assumed for elderly as defined previously in young subjects.

Linear regression was performed to derive descriptive, continuous equations from 20 to 99 years for the parameter of interest considering the independent covariates age, sex, anthropometric parameters, study location and publication year. Several data transformations, such as log-transformation, were investigated during regression analysis. Covariates with a p-value below 0.01 were considered as significant. The regression with the smallest sum of residuals was used. The performance of each derived equation was checked with an independent verification dataset. Variability for each parameter was calculated as the weighted coefficient of variance of the development dataset.

Results:

A total of 362 studies were found and finally 318 studies were included in the analysis adequately describing 44 out of 60 model parameters. Rich data were found for anthropometric parameters and for some organs, e.g. kidney and liver. Data for some regional blood flows, such as to the bone, and in general composition of tissues, were difficult to obtain from the literature and values for young subjects were required to be used. For tissue composition, the predicted sum of water and cell mass for all tissues assuming age-independent fractions coupled with age-dynamic tissue volumes were in accordance to reported total body water and total body cell mass showing the plausibility of used assumptions.

The developed population has been implemented in Matlab® and 1000 virtual men and women have been created. The estimated body height, body weight, organ weight, blood flows, plasma-binding protein

concentration and glomerular filtration rate were in accordance to the independent verification dataset, demonstrating robustness of the developed population.

Conclusions: The developed population database for aging subjects can be implemented into existing PBPK frameworks and could subsequently allow the prediction of drug kinetics and drug-drug interactions in elderly.

Although including data for centenarians, most of the data were found from studies up to the mid-eighties identifying a knowledge gap for older individuals. It is worthwhile mentioning that for some parameters like blood weight, only data from the United States and studies published 50 years ago were found. The impact of location and publication year has been checked on the well described anthropometric parameters. Publication year was found to be a significant covariate for body weight, explained by a significant increase in body weight of adults over the last decade. This argues for the necessity to constantly update PBPK models and include body weight as a necessary covariate in the development dataset.

The developed repository provides continuous functions to describe anatomical and physiological system parameters from the age of 20 to 99 years, considers population variability and includes studies on the age-dependency of metabolising enzymes and drug transporters.

I-18: *Konstantinos Stamatopoulos* A Population based PBPK Modelling for the Prediction of Bile Salts Disposition within GI Luminal Fluids – Towards a Mechanistic Bile Salts Model

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Objectives: Bile salts (BS) play a crucial role in the solubilisation and the absorption of lipophilic and poorly soluble drug compounds. The concentration of BS, however, varies significantly within the GI tract due to a number of factors such as cyclic motility patterns of gall bladder (GB) linked to the interdigestive migrating motor complexes (IMMC) [1,2], dynamic changes within the GI luminal fluids and most importantly the prandial state. As opposed to the fasted state, strong GB contractions empty a significant amount of BS in response to the feeding events. Thus, a novel mechanistic BS model was developed and coupled with a previously developed dynamic GI fluid volumes model [3], to predict the intestinal BS concentrations as a function of time and prandial status.

Methods: The distinctive characteristics of the model include the generation of individualised IMMC cycle patterns; IMMC associated GB filling and emptying phases; hepatic bile acid mass secretions rates and regional bile acid absorption kinetic parameters. The number of IMMC events within 24 hours, duration of the IMMC cycle based on its origin, either from stomach or duodenum, and their corresponding proportions is defined priori for every individual. The Model also accounts for the inter-individual GB volumes (GBV); Initial amount of bile acid in GB (mmol); and GB residual volume in the fasted and high-low-fat meals. The GB filling phase takes place during the 0–30% of the IMMC cycle followed by an emptying phase that terminates at 60% or 90% of the IMMC cycle depending on where it had a duodenal or antral origin respectively. Using this relationship, the individualised GB filling-emptying cycles could be generated according to the number of IMMC events taking place per 24 hour period. Within the model, the GB filling rate is linked to the hepatic bile secretion rate (mL/h). Thus, the hepatic bile flow rate is back-calculated from the slope of the linear regression of GBV vs IMMC cycle time during the filling period. In the fed state, the GB contracts strongly, emptying a significant proportion of its content (ejection fractions can reach 95% [4] compared to 30% in the fasted state [2]). Furthermore, the GB empties its content within an hour of the meal ingestion followed by a refilling period which can last up to ~6 h [4] after which the cyclic fasted GB motility profile is restored. The total bile mass secretion in the duodenum is assumed well mixed with the dynamic luminal fluid volume and thus can predict the time dependent BS concentration within the GI tract. The model includes re-absorption of BS from the luminal fluids and kinetic parameters defining passive (jejunum and colon) and/or active (ileum) components has been used. The performance of the proposed model was assessed by comparing the predicted BS concentration with those reported from *in vivo* studies [5].

Results: Twenty-four hours fasted motility profiles of the GB were generated together with a meal ingested at a random time during this period. The results of the simulations using 1000 virtual individuals showed cyclic fluctuations of BS concentration in the duodenum, with ranges of 0.25-37 mM (fasted) and 0.45-48 mM (fed) which is within the ranges reported in the in vivo studies (fasted: 0.03-36.18 mM; fed: 0.74-86.14 mM, [5]). Multiple minor peaks were also observed in the duodenal fluid volumes, following the discontinuous release of biliary secretions. However, these peaks are diminished as moving towards ileum compartment. Similar results have been reported from MRI studies, showing time-dependent fluctuations of intestinal fluid volumes which in part can be attributed to the bile fluid dynamics [6, 7].

Conclusions: Quantitative estimation of time dependent BS concentration within the GI tract is critical for the accurate prediction of oral drug absorption within the PBPK modelling framework. The developed dynamic BS model, coupled with GI fluid dynamics, could successfully describe the multiple BS peaks observed within the in vivo study [1] and also predicted the BS concentrations within the known physiological range [5]. This dynamic model would also form a basis of mechanistic enterohepatic re-circulation of drug and/or metabolites modelling within the PBPK framework.

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I-19: *Andrew Stein* Guiding dose selection of monoclonal antibodies using a new parameter (AFTIR) for characterizing ligand binding systems

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Objectives:

In guiding dose selection for monoclonal antibodies, the methods for predicting receptor occupancy (RO) vary in their level of complexity.

A simple approach was used for atezolizumab [1]. This approach asserted that the following equation held for predicting RO in a tumor: RO = B·Cavg/(B·Cavg + Kd), where B is the fraction of drug from circulation that makes it to the tumor, Cavg is the average drug concentration at steady state (trough concentration could also be used), and Kd is the dissociation constant for the drug. This equation was used without a clear statement of all assumptions needed; in particular, using Kd implicitly assumes that receptor internalization and shedding are unimportant.

A more complex approach was used for pembrolizumab [2]. Here, a physiological model for drug distribution was combined with a receptor binding model and a tumor kinetic model. In this case, all assumptions were clearly stated, but the model was more complex than necessary and this complexity can make it challenging to mathematically understand the model and to explain it to decision-making boards that are unfamiliar with quantitative systems pharmacology.

In this work, we derive a simple expression for target engagement for a physiological model of drug distribution and target binding and we show that this simple expression accurately approximates target engagement for the more complex physiological model. This expression is more accurate than the RO equation above and is easier to explain than the full physiological model.

Methods:

A new parameter was recently derived for characterizing target engagement in circulation for the standard target mediated drug disposition (TMDD) model [3]. Here, this work is extended to estimate the Average Free Tissue target to Initial target Ratio (AFTIR). The extended model includes distribution of the drug and target from circulation to the tissue of interest, binding of the drug to both a membrane-bound and soluble receptor, shedding of receptor from the cell surface, and elimination of both drug, target, and complex. A mathematical derivation of AFTIR is shown and simulations using realistic parameters for trastuzumab, atezolizumab, pembrolizumab, and bevacizumab were performed to check that AFTIR accurately characterizes target engagement.

Results:

The following equation holds under the assumptions listed further below.

AFTIR = Tavg/T0 = Kssd·Tfold/(B·Cavg)

Tavg is the free target concentration at steady state; T0 is the baseline target level in tissue; Kssd is the steady state binding coefficient with distribution (defined further below); Tfold is the fold-change of target in tissue upon binding the drug; and B and Cavg are as described above. Analytical expressions for each of the terms were calculated explicitly from the system parameters and dosing regimen.

The steady state binding coefficient with distribution is given by Kssd = (kint + kshed + kdist + koff)/kon, where kint is the drug-target complex elimination rate; kshed is the complex shedding rate (for membrane-bound targets, zero otherwise); kdist is the rate of distribution of the complex from tissue back to circulation; and koff and kon are the unbinding and binding constants. When kdist=kshed=0, then Kssd=Kss, the steady state binding constant [4]. When koff >> kint + kshed + kdist and when Tfold = 1, this formula agrees with the simpler RO equation from [1].

The expression above requires the assumptions that the tumor can be treated as a homogenous tissue, and that the drug concentration in the tissue of interest is much larger than the target concentration. When these assumptions are met, simulations of target engagement for the full physiological system matched the AFTIR equation. To apply this equation in practice, additional assumptions are often needed, including estimates for B, Tfold, and the value of AFTIR needed for efficacy.

Conclusions:

To predict target engagement in the tissue of interest, a simple equation for AFTIR has been derived and the set of assumptions needed to apply this equation have been provided. This simple expression shows how four lumped parameters: Kssd, Tfold, B, and Cavg impact target engagement and this formula together with the necessary assumptions can be used to guide Phase 2 dose selection for a monoclonal antibody. This methodology can be readily explained to decision making boards and is more accurate than the simple receptor occupancy equation used previously [1].

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I-20: *Mark Stroh* Customizing the distribution of a masked, tumor-activated antibody with quantitative systems pharmacology

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Objective: Probody™ therapeutics (Pb-Txs) are masked monoclonal antibody (mAb) prodrugs designed to be preferentially activated by tumor-associated proteases. The peptide mask inhibits binding of the Pb-Tx in healthy tissues and, when removed by tumor-associated proteases, releases an active mAb. The aim of this study is to develop a quantitative systems pharmacology (QSP) model that integrates Pb-Tx and system properties for controlling Pb-Tx distribution. The Pb-Txs evaluated in this investigation were directed against activated leukocyte cell adhesion molecule (ALCAM; CD166), which is highly expressed in both tumors and healthy tissue.

Methods: A QSP Pb-Tx model was developed, calibrated against cynomolgus monkey pharmacokinetic (PK) data, and used to project human PK and pharmacodynamics (PD). Whole blood was collected from cynomolgus monkeys at various timepoints up to 21 days post-dose following administration of anti-CD166 Pb-Txs with varying mask and substrate characteristics. Dose levels investigated included 3, 5, and 10 mg/kg administered either as a single dose or as two doses administered three weeks apart. Models were implemented using KroneckerBio v. 0.4 (https://github.com/kroneckerbio) and expressed as a system of ordinary differential equations with the following form:

$$dx/dt=k+Ax+B\,(x\otimes x)$$

where k is a vector of 0th order rate constants, A is an n by n matrix of 1st order rate constants, and B is a n by n matrix of second order rate constants. Parameter estimation and simulations were performed using MATLAB v. 2015b (Mathworks, Natick MA).

Results: The QSP Pb-Tx model was developed to capture events both at the Pb-Tx and the compartmental levels. The QSP Pb-Tx model has provisions that are unique to the Pb-Tx as well as those that are shared with other mAb pharmacology models. Elements shared with mAb pharmacology models include those governing mAb distribution both in the systemic compartment (1, 2) and in the tumor (3), including those governing receptor binding, and receptor and receptor-drug complex endocytosis. These events in turn occur downstream of Pb-Tx administration, distribution, and activation by proteases(4).

The QSP Pb-Tx model adequately described monkey PK data following administration of six Pb-Txs of different mask strength and protease substrate cleavability. The QSP Pb-Tx model suggested decreasing importance of target-mediated drug disposition with increasing mask strength, and captured the corresponding, observed trends of decreasing systemic clearance. Simulations in humans suggested increasing levels of activated Pb-Tx in tumor in comparison to simulated exposures following administration of the corresponding, unprotected parental mAb. The QSP Pb-Tx model suggested an optimal mask strength for maximizing tumor receptor-mediated uptake. Simulations further suggested that the Pb-Tx would circulate predominantly as the masked, intact species. Under physiologically-relevant conditions, QSP Pb-Tx model simulations did not project significant tumor flux of activated Pb-Tx to the systemic compartment.

Conclusions: The QSP Pb-Tx model captures the determinants of Pb-Tx PK/PD, allowing for customizable Pb-Tx distribution even with a broadly-expressed target like CD166.

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I-21: *Sabine Stuebler* Systems biology model of the mucosal immune system in the context of inflammatory bowel disease

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Objectives: Inflammatory bowel disease (IBD), with its major forms Crohn's disease and Ulcerative colitis, is a chronic disease caused by autoimmunity of T cells against commensal bacteria in the gut. Current treatment regimens include corticosteroids, immunomodulatory small molecule drugs and monoclonal antibodies (mAbs) targeting TNF-a, but the therapeutic outcome differs highly between patients. A better understanding of the mucosal immune system in the context of inflammatory bowel disease is therefore highly desirable. The objective of this work was to mathematically describe the cellular processes of the intestinal immune system to provide a basis for further analysis of drug effects and inter-individual variability.

Methods: We identified important processes of the mucosal immune system (innate and adaptive) on the cellular level through an extensive literature research. These processes were described (i) in terms of literature values as parameters, (ii) by fitting parameters to literature data from human, mouse or in vitro studies, or (iii) by assuming reasonable parameter ranges resulting in adequate model behaviour, where literature data were not available. We combined these processes into a systems biology model that described concentrations of several cell types in the gut lamina propria and the mesenteric lymph nodes.

Results: The developed ODE model included dendritic cells, (naive, memory, helper and regulatory) T cells, macrophages, neutrophils and bacterial cells. Dendritic cells in the lamina propria were present in four different states depending on their inflammatory status and uptake of antigen. Macrophages in the lamina propria were modelled by transitional compartments, from a pro-inflammatory to anti-inflammatory status (as shown in [1]). Neutrophils were recruited when bacteria penetrated into the lamina propria and died from apoptosis, where apoptotic neutrophils increased neutrophil apoptosis and inhibited neutrophil recruitment, resulting in self-limiting neutrophil invasion. Bacterial killing by neutrophils, dendritic cells and macrophages was modelled by using a maximal killing rate per phagocyte, resulting in a critical phagocyte concentration needed for bacterial elimination (as proposed by [2]). In the mesenteric lymph nodes dendritic cells presenting bacterial antigen activated naive and memory T cells expressing the specific T cell receptor, which differentiated into helper T cells that further stimulated the innate immune system or regulatory T cells that limited the extent of the inflammation. As their half-lives are comparably small on the time-scale of the modelled cells, pro-inflammatory and anti-inflammatory cytokines were included implicitly in the model, as linear combinations of the producing cells. Pro- and anti-inflammatory cytokines were assigned opposing effects in the activation of dendritic cells and in the de-activating transition between macrophage subsets. In addition, pro-inflammatory cytokines increased leukocyte recruitment into lamina propria.

The model was able to reflect the main characteristics of the mucosal immune system: Bacteria up to a threshold concentration were efficiently cleared in the model. As first line of defence neutrophils infiltrated the lamina propria, dendritic cells and macrophages followed. Dendritic cells and macrophages shifted to an inflammatory state upon activation and recovered when the bacteria were eliminated. Effector T cell

concentrations increased with a delay. After the acute inflammation all cell concentrations returned to baseline.

Regarding the aim of describing the cellular dynamics in IBD, we identified several steps that are further required. Different IBD triggers known from literature will be translated into model inputs and tested for the result of chronic inflammation in the model. A virtual population of patients will then be generated by different trigger combinations leading to chronic inflammation. To simulate treatment, drug PK and actions will be included (e.g. anti-TNF-alpha mAbs and interaction with TNF-alpha).

Conclusions: The developed systems biology model was able to reflect the main characteristics of the mucosal immune system. This is a promising first step towards modelling the pathological processes and drug effects in IBD.

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I-22: *Claudia Suenderhauf* The Basel Phenotyping Capsule as a tool for Quantifying Human metabolism in vivo – a tool to personalize physiological and semiphysiological Models

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Objectives:

Cytochrome P450 (CYP) enzymes are the main metabolic pathway of numerous endogenous and xenobiotic compounds. Hence, estimates of CYP activity is relevant for clinical decision making in drug therapy as well as in drug development. Drug interactions and disease states, such as inflammation or chronic liver disease, potentially alter CYP function substantially, regardless of the underlying genotype. Altered CYP function may result in changed systemic drug exposure, which in its extremes causes either increased pharmacodynamic effects, even toxicity or therapeutic failure. Hence, attempts were made assessing CPY phenotype for estimating metabolic capacity in humans in vivo. The application of CYP isoform specific probe drugs has been shown to be a safe and reliable phenotyping test: By calculating the ratio (i.e. the metabolic ratio, MR) between concentrations of parent drug and metabolite the capacity of CYP under investigation can be assessed [1][2]. As we have shown, quantitative ranking of metabolism status can be done by putting MRs in relation to ratios obtained in induced and inhibited states [2]

We selected and tested 6 CYP isoform-selective probe drugs in a clinical trial, combined in a single capsule, to reduce drug amount to low- or even micro-doses and to allow a convenient administration [3]. The aim of the present study was to select CYP isoform-selective probe drugs, combined in a single capsule and obtain PK profiles in healthy volunteers, check for tolerability, and calculate MRs. In addition, we aimed to determine a reduced optimal sampling regimen for the newly defined probe drug cocktail.

Methods:

We performed an open-label randomized 2-period crossover PK study in 12 healthy volunteers using the Basel phenotyping cocktail capsule. Non-compartmental analysis was performed for each compound using R to obtain basic PK parameters and calculate MR for each sampling time point and $AUC_{0\text{-}12h}$. As a preliminary analysis, we fitted a linear model to determine sampling time points which correlate best with MRs calculated of $AUC_{0\text{-}12}$.

Results:

Six substances, namely caffeine, efavirenz, flurbiprofen, metoprolol, midazolam and omeprazole were combined in a capsule formulation and administered to 12 healthy volunteers. PK profiles from parent compound and metabolite were obtained and a non-compartmental analysis was performed. MRs of single TP measurements as well as MRs of $AUC_{0\text{-}12h}$ were calculated. We found for caffeine (CYP1A2) and flurbiprofen (CYP2C9) one subject with rapid metabolizing phenotype, while for metoprolol (CYP2D6) there was one poor metabolizer phenotype. However, Hartigans' Dip Test for Unimodality showed a unimodal distribution of AUC MR for all compounds in our dataset [4]. We hence concluded that we had no significant subgroups of rapid or poor metabolizers for any CYP among our sample, except these 3 individuals.

Because of large differences in PK profiles, sampling timepoints could not be collapsed to a single measurement. MRs at 2h correlated best with midazolam (CYP3A4, adj.R2: 0.89, $p < 0.001$) and caffeine (CYP1A2, adj.R2: 0.94, $p < 0.001$) AUC ratios, while for efavirenz (CYP2B6, adj.R2: 0.85, $p < 0.001$), flurbiprofen (CYP2C9, adj.R2: 0.99, $p < 0.001$), and omeprazole (CYP2C19, adj.R2: 0.85, $p < 0.001$) best fits were achieved at 6h. Metoprolol showed excellent fits at both of these timepoints (adj.R2: 0.99, $p<0.001$).

Conclusions: The phenotyping approach was shown to be well tolerated by all subjects and easy to perform. The information of such experiments is valuable to individualize and inform physiological and semiphysiological Models. Further studies are currently ongoing in our group to characterize patients at different stages of liver cirrhosis by means of the Basel Phenotyping capsule. In a next step, we plan to adapt a Population Optimum Design of Experiments (PODE) approach to predict MR_{AUC} from a minimum of PK samples.

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I-23: *Elin Svensson* Meta-analysis of rifampicin exposure and mortality in three randomized controlled phase II tuberculosis meningitis trials

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Objectives: Tuberculosis meningitis (TBM) is the most severe form of tuberculosis, with up to 50% mortality mostly within the first 2 weeks after presentation of disease [1]. The currently recommended antimicrobial treatment for TBM is the same as for pulmonary tuberculosis and consists of a 4-drug combination: rifampicin (RIF), isonizid, ethambutol and pyrazinamide. Recent studies suggest that an intensified regimen with higher rifampicin doses during the first critical days of treatment may improve the outcome of TBM. The objective of this work was to characterize the population pharmacokinetics (PK) of high-dose RIF in plasma and cerebrospinal fluid (CSF), investigate predictors of PK variability and evaluate a link between individual RIF exposures and mortality during the first 6 month of treatment in an individual patient data meta-analysis.

Methods: Data originated from three randomized controlled phase II trials preformed in the same center in Bandung, Indonesia [2-4]. The studies compared the standard RIF oral dose of 450mg to intensified 14 or 30-days regimens including 750, 900 or 1350mg oral RIF, or an intravenous RIF infusion (1.5h) of 600mg. Rich plasma PK sampling were performed at day 2±1 and for two of the studies also at day 12±3. A single lumbar puncture was performed at PK days for quantification of RIF and metabolites in CSF as described in the original publications [2-4]. The 6-month survival was captured and described with time-to-event models. The exposure-response analysis was preformed sequentially using NONMEM 7.3.

Results: The PK dataset included 133 individuals and 1266 RIF observations of which 1150 (170 from CSF) were above the limit of quantification and included in the fit. The final model included absorption through a chain of transit compartments, a well-stirred liver model [5], and two disposition compartments. Intrinsic clearance (CL_{int}) was saturable following Michaelis-Menten kinetics [5, 6]. RIF's autoinduction was accounted for by a separate CL_{int} estimated for late samples (after day 7) and found to be 49% (95% confidence interval 27-71) higher compared to during the first days. The bioavailability of a 450mg dose was estimated to be 72% (62-82), and increased nonlinearly with dose as previously described [6]. The volume of distribution was found to be 19% (12-27) lower at late time points, potentially reflecting an improvement in disease status. Allometric scaling with fat-free mass and fixed coefficients was included on all disposition parameters.

RIF CSF concentrations were modeled with a partition coefficient and a half-life for the distribution between plasma and CSF [7], estimated to be 5.5% (4.5-6.5) and 2.1 (1.3-2.9) hours, respectively. Addition of inter-individual variability in the partition coefficient was statistically significant and estimated to be 37%CV. Measured protein concentration in CSF was a significant covariate on the partition coefficient, with higher protein concentration correlated to higher CSF RIF concentrations.

The survival dataset included 148 individuals of which 58 died and 15 dropped out before 6 months. The hazard model that best described the survival was a exponentially declining function (deltaOFV -91.2 and -24.3, compared to constant and Weibull functions, respectively).

The effect of individual RIF exposure (plasma and CSF $AUC_{0\text{-}24h}$ and plasma C_{max}) on the hazard was evaluated with linear, power and E_{max}-relationships. Plasma $AUC_{0\text{-}24h}$ was the best performing exposure metric and the effect on the hazard was coded as follows:

$h_i = h_b * (1 - AUC_i/(AUC_{50} + AUC_i))$

An estimated maximal effect did not improve the model, nor did a different effect for 14 or 30 days of intensified treatment. The AUC_{50} was estimated to be 161 mg/L*h, the observed range of RIF $AUC_{0\text{-}24h}$ was 1-486 mg/L*h. Simulations predicted the mortality to decrease from 49.6% as expected with the 450mg dose (median exposure 48 mg/L*h), to 30.5% expected with the 1350 mg dose (233 mg/L*h).

Conclusions: This individual patient data meta-analysis showed that higher RIF exposure during the first 14 days of treatment substantially decreased the risk of death in Indonesian TBM patients. Maximal effect was not reached within the studied range of exposures, indicating that doses even higher than 1350 mg could bring additional benefits if they can be safely administered. The optimal dose of RIF in treatment of TBM should be further investigated in phase III type trials.

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I-24: *Robin Svensson* The value of model-based therapeutic drug monitoring in tuberculosis treatment – optimized target for rifampicin

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Objectives: This work evaluated a Bayesian model-based therapeutic drug monitoring (TDM) approach for rifampicin accounting for the known auto-induction and dose non-linearity in bioavailability.

Methods: Thirty-three patients treated for tuberculosis in Sweden were given rifampicin at 10 mg/kg as part of standard multi-drug therapy. Rifampicin plasma concentrations were measured at pre-dose and following 2, 4 and 6 hours post-dose after two weeks of treatment. Rifampicin plasma concentrations were also quantified at pre-dose and at 2 hours at weeks 4 and 12.

A new optimized TDM target for rifampicin of day 14 maximal concentration ($C_{max,\ D14}$) of 35 mg/L was identified in a dose-ranging clinical trial using the observed geometric mean of $C_{max,D14}$ following 35 mg/kg rifampicin, a dose which was found to have no safety concern [1]. C_{max} was preferred over AUC as the target pharmacokinetics (PK), due to the post-antibiotic effect of rifampicin, where effect is most closely associated with C_{max} and not AUC [2].

A Bayesian model-based TDM dose was derived for each patient by using a previous rifampicin PK model accounting for auto-induction and dose non-linearity in bioavailability for high dose rifampicin [3]. First, individual PK parameters for each patient was obtained through a Bayesian step using all individual data and the PK model using fixed and random parameters Inter-occasion variability was included in the estimation of individual PK parameters.

Secondly, the individual PK parameters were used to predict the Bayesian model-based $C_{max,D14}$ following higher doses of 15-50 mg/kg. The highest dose not exceeding the TDM target $C_{max,D14}$ of 35 mg/L, was predicted for each patient.

The simulated PK summary indices (C_{max} and $AUC_{0\text{-}24h}$) at day 14 were summarized for each dose level and compared with literature values [1] and related to the expected relative change in exposure if non-linear elimination was not present.

All estimations and simulations were performed in NONMEM 7.3 [4]. The M3 method was used to handle samples below the lower limit of quantification. A visual predictive check (VPC) was performed to evaluate the predictive properties of the model to describe the 10 mg/kg dose level.

Results: A total of 224 samples were included in the analysis of which 34.4% (77 samples) were below the lower limit of quantification. A VPC based on all the observed pharmacokinetic data stratified on day of treatment indicated that the model was able to describe the observed data well.

The Bayesian model-derived TDM dose in this patient population ranged from 20-45 mg/kg (mode 25 mg/kg) in order to meet the TDM target $C_{max,D14}$ of 35 mg/L which is due to the higher clearance in this patient population compared to the population that was used to define the target [3].

The predicted values for C_{max} and AUC_{0-24h} at day 14 agreed well with published values of increasing doses of rifampicin indicating the similarity of this subpopulation compared to the subpopulation used to build the model [1, 3]. The predicted relative increase in AUC_{0-24h} for 35 mg/kg compared with 10 mg/kg was 5.3 times higher, which is higher than to be expected under the assumption of linear PK.

Conclusion: Model-based TDM is warranted for dose optimization and personalised medicine for rifampicin due to its complex PK which makes predictions of individualized dosing impossible unless a model based approach is used. This study shows that the applied population PK model is optimal for TDM of rifampicin and that a new optimized TDM target of $C_{max,D14}$ of 35 mg/L would lead to a dose with optimized effect on an individual patient level.

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I-25: *Elisa Tacconi* Model-based analysis for the screening and ranking of compounds against Plasmodium Falciparum

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Objectives: Malaria is a serious tropical disease caused by infection with *Plasmodium protozoa* that are transmitted by *Anopheles* mosquito bite. Five different species of *Plasmodium* infect humans with severe disease, but human malaria is primarily caused by *Plasmodium Falciparum*. When the mosquito bites humans, the parasite is released into human bloodstream [1]. The role of malaria on the developing world is huge, and a fully protective vaccine is still missing. One of the biggest challenges for the development of new antimalarial drugs and vaccines is the lack of accessible animal models to study *P. Falciparum* infection because the parasite is restricted human erythrocytes hosts. In this project, I developed a pharmacodynamics "humanized" mice model that describes the infection cycle of disease and the drug effect to select antimalarial compound with higher efficacy [2]. The main aim of the study was to develop a drug-disease model for the screening and ranking of compounds against *Plasmodium Falciparum* based on efficacy parameters.

Methods: Preclinical data was obtained from *in vivo* experiment done on "humanized" mice (mice engrafted with human erythrocytes) infected by *P. Falciparum*. Data was obtained from experiments in which *four* different anti-parasitic compounds were tested according a specific experimental protocol. All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals. For the estimation of drug-effect parameters was used a population modelling approach, the analysis was carried out in NONMEM V7.3 [3]. The data was first analysed and rearranged to allow the readability in NONMEM, data manipulation was performed using R V3.0.1 and R Studio user interface. The estimation methods used were FOCE with interaction and LAPLACIAN [4]. The model prediction ability was verified using goodness of fit and validation criteria. The ranking compounds was based on estimated efficacy parameters.

Results: It was used a compartmental pharmacodynamics model to describe data. The use of a compartmental model-based approach proved to be appropriate to mechanistically describe the life cycle of parasite. The model predicts the number of parasites inside the humanized mice blood for each tested compound until 30 days after infection to predict the recrudescence (recurrence of symptoms after a quiescent stage). The $EC_{50KDEATH}$ was selected as the efficacy parameter to base the compound ranking for the precision in describing the level of parasitemia (number of parasites) in mice blood.

Conclusions: The pharmacodynamics mice model allows the screening and ranking of compounds against *Plasmodium Falciparum*. The compound ranking is based on direct killing parasites drug action. The model could also predict the recrudescence of parasite and could be applied in the future for a more accurate and extended classification of compounds and could provide the basis for a possible dose in humans.

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I-26: *Chong Tang* Population Pharmacokinetics of Tacrolimus in Pediatric Patients having undergone kidney, liver or bowel/liver transplantation.

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Objectives: Multiple clinical, demographic and genetic factors affect the pharmacokinetics (PK) of tacrolimus (Tac), necessitating therapeutic drug monitoring (TDM). Due to profound changes in age and size over the course of treatment in the pediatric population (a child can easily double its weight while on maintenance therapy with Tac), a thorough assessment of covariate effects, the projected change of dose with age/size and quantification of the remaining within and between subject variability (WSV, BSV) is warranted, but usually prevented by a small number of patients, brief follow up and lack of diversity of covariates in the analysis datasets. Recently, a distinct age effect on top of weight/BSA on the dose exposure relationship has been postulated in 43 renal transplant patients, using full AUCs as summary metric of exposure [1]. We applied nonlinear mixed effects modeling on individual concentration time courses from this meanwhile extended and growing database.

Methods: The analysis dataset grew from 43 [1] to 79 stable post-transplant patients (renal: 51 (64.5%), liver: 26 (33%), bowel/liver: 2 (2.5%); donor status: 73% deceased, 27% live) included between 1998 and 2017. At time of inclusion (first PK assessment) patients were aged from 1.3-20.7 ys (median=11.3ys), weighing between 9.9-75.5 kg (median= 32.7 kg). CYP3A4-1b, CYP3A5 and CYP3A7 pharmacogenetic information was dichotomized according to the known influence on Tac metabolism (i.e. fast (F) and slow (S) metabolizers (M)). 14% of patients were FM for CYP3A5, 2.5% were FM for both CYP3A4 and CYP3A7. 1-14 (median=4) concentration time course per patient ("occasions") were available, spaced between 10d to 11.3ys (median 1.0 ys) post transplant. Per occasion, 6 Tac steady state concentrations were collected (0, 1, 2, 4, 6 and 12h), covering the entire interdose interval. The analysis was performed with MONOLIX 2016R1. Compartmental models with first order input into a depot and lag time were tested. Covariate exploration was done treating each concentration time course as a (virtual) individual and repeated with the definitive model including a full covariance matrix for volumes and clearances for both BSV and WSV. Improvement of -2LL, visual inspection and standard errors of the parameters were used for judging goodness of fit and covariate inclusion/deletion.

Results: A two-compartment model with first-order absorption and elimination adequately described the concentration time course of Tac. CYP3A5 fast metabolizers and fast metabolizers for both CYP3A4 and CYP3A7 displayed similar CL values and were lumped into one group (22% increase in CL). Tlag and ka did not differ much between models and were approx. 0.45 h and 0.65 1/min. Volumes and Clearances of the final model are for a weight of 70kg, a hematocrit of 40%, slow metabolizers and, where applicable, an age of 20ys. The allometric coefficients for weight on V1, V2, CL and Q for the final model were (TV+SE): 0.54 (0.16), 0.55 (0.11), 0.45 (0.05) and 0.51 (0.08).

Table: Parameters (TV+SE, random effects (BSV/WSV, SD in log domain)) and significant covariates (p<0.01)

	TV(SE, BSV, WSV)

Model	V1 [L]	V2 [L]	CL [L/h]	Q [L/h]	covariates	OFV
"virtual ind." base	53 (6.3, 1.23,-)	533 (47, 0.58,-)	22.1 (0.63, 0.57,-)	76.3 (4.1, 0.64,-)	-	10687
"virtual ind." final	60.2 (1.19, -)	842 (0.6,-)	24.7 (0.45,-)	94.4 (0.53,-)	WT on V1,V2, CL,Q; Hct+CYP on CL, Age on V1, Q	10490
"correct" base	76.7 (9.4, 0.65, 1.04)	401 (32, 0.46, 0.42)	21.6 (1.3, 0.5, 0.31)	73.4 (5.5, 0.50, 0.52	-	10357
"correct" final	86.1 (14, 0.6, 0.98)	590 (67, 0.4. 0.4)	24.2 (1.4, 0.38, 0.30)	94.8 (7.9, 0.41, 0.42)	WT on V1, V2, CL, Q; Hct+CYP on CL	10256

Conclusions: Size, hematocrit and enzyme activity are the major covariates to be considered in Tac open loop dose adjustment. Unexplained BSV/WSV on CL with the best model are 38% and 30%. The allometric coefficients for clearance were significantly smaller than 0.75 (0.56, 0.45, SE's 0.05 for both) and we concur with the recommendation for body surface area based dosing by Knops et al [1]. Age was not identified as a covariate in the final analysis, confirming the results of [2,3] and contrary to [1]. Due to mandatory TDM adjusted dosing, this is inconsequential for adjustments of maintenance doses. Care must be taken when deciding on a covariate identification strategy in large unbalanced datasets containing covariates changing per individual and covariates changing per occasion.

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I-27: *Lénaïg Tanneau* Bedaquiline appears to antagonize its own main metabolite's QTcF interval prolonging effect

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Objectives: More than 40 years after rifampicin's discovery, bedaquiline (BDQ) was the first anti-tuberculosis drug with a novel mechanism of action that received accelerated approval by the US FDA in 2012 for the treatment of multidrug-resistant (MDR) tuberculosis (TB) in adults as part of combination therapy [1]. It has been shown that BDQ shortens the time to sputum culture conversion and increases the cure rate [2]. On the other hand, administration of BDQ may lead to prolongation of the heart's QT interval, which is a safety concern since patients can develop cardiac arrhythmias such as Torsades de Pointes (risk factor of sudden death) [3].
The objective of this study was to investigate potential relationships between concentrations of BDQ and/or its main metabolite (M2) and QTcF interval (QT interval corrected with Fridericia's coefficient) in MDR TB patients using the approved BDQ dose regimen.

Methods: Data were obtained from two phase IIb studies (C208 [3] and C209 [4]) and were pooled to include a total of 335 patients treated with BDQ and 105 patients with placebo. Patients were newly diagnosed (all C208 patients and 10% of C209 patients) or treatment-experienced subjects and received BDQ (200mg qd for 2 two weeks, then 400mg tiw) or placebo for 24 weeks (or 8 weeks in stage 1 of C208) in combination with a background regimen of 5-7 anti-TB drugs. Pre-dose BDQ/M2 PK samples were drawn at 7 occasions in all patients of the placebo controlled C208 study and full PK profiles performed at week 2, 8 and 24 (stage 1) or week 24 (for a subset of patients in stage 2). The open-label C209 study included 3 pre-dose samples per patient (week 2, 12 and 24). Single ECGs were performed weekly while triplicate measurements at pre-dose and 5 hour post-dose were taken at week 2, 8, 12 (only C209) and 24. The trials were conducted in accordance with Good Clinical Practice standards and received ethical approval from appropriate local authorities.
Since a PK-model for BDQ and M2 was previously established for these trials [5], a sequential approach was used. The individual model-predicted BDQ and M2 concentrations were evaluated as predictors (covariates) in the development of the pharmacodynamic (PD) model for QTcF interval. The effect of the presence/absence of background regimen also was explored.

Results: 14263 observations of QTcF interval were recorded at baseline (just before start of study treatment) and during the treatment period. The baseline QTcF of 399 ms (without any TB treatment) increased by 0.8 ms in the presence of background regimen in C208 study and by 4.19 ms in C209 study. After testing separate drug effects for BDQ and M2 (on/off, linear, Emax, sigmoidal Emax), as well as full and partial competitive agonist models, the model that best described the data during the treatment period was a competitive antagonist model [6, Eq 3:49]. Thus, BDQ appears to act as an antagonist of M2 effect and has no intrinsic activity (i.e. $E_{max,BDQ}$ is zero). Related parameters were estimated at 12.9 ms (RSE 5%) for $E_{max,M2}$, and at 229 ng/mL (RSE 8%) for $EC_{50,BDQ}$ and 14 ng/mL (RSE 6%) for $EC_{50,M2}$. This model performed better than Emax effect models of BDQ and M2 alone, by 1255 and 160 points drop in OFV, respectively. In addition, analysis of each study data separately (C208 and C209) showed robustness of the results (pharmacologic mechanism and parameters estimates).
This would mean that the QT prolongation is driven exclusively by M2 concentrations while BDQ

antagonizes the effect of M2 on QT prolongation. The interaction of both BDQ and M2 at the same target is supported by results from pre-clinical studies, where both inhibit IKr channel (known to cause prolonged QT) in hERG transfected kidney cells. However, the relative magnitude of each effect could not be quantified in vitro [7].

Conclusions: The QTcF interval prolongation observed in the phase IIb studies of BDQ was explained by an effect of the background regimen and M2 exposures, while BDQ antagonizes the effect of M2. A QTcF model can together with previously developed models for population PK [5] with drug-drug interactions [8–12], and sputum conversion [13], inform an integrated dose-exposure-efficacy-safety analysis of BDQ.

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I-28: *Sonya Tate* Dose Fractionation Study Design and PK/PD Model Analysis to Establish the Quantitative Pharmacology of Selective Aurora A Kinase Inhibition by Compound X and LY3295668

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Objectives: During early drug discovery, characterising the quantitative pharmacology of early tool compounds is an important component of candidate design and selection. By understanding the desired extent and duration of target engagement, project teams can better select the pharmacokinetic / pharmacodynamic (PK/PD) properties to optimise, resulting in clinical candidates with a higher probability of success. Furthermore, once the pharmacology of a tool compound has been evaluated, the behaviour of each emerging candidate of interest need only be confirmed with streamlined, targeted study designs. The objective of this work was to quantify the extent and duration of selective Aurora A inhibition required for tumour shrinkage using a tool compound (Compound X), and to translate these findings to emerging Aurora A inhibitors of interest, of which LY3295668 was ultimately selected for progression to the clinic.

Methods: To evaluate the extent and duration of selective Aurora A engagement required for tumour shrinkage, a dose fractionation study design was employed. Using a 40 mg/kg total daily dose as a guide, Compound X was administered orally to xenograft tumour-bearing mice at 10 mg/kg QID, 20 mg/kg BID and 40 mg/kg QD for 14 days, with an additional comparison group at 40 mg/kg Q2D, with drug plasma concentration, biomarker (phosphorylated Aurora A; p-AurA) and tumour size data collected throughout the study period. The resulting data were analysed in a sequential manner using empirical PK, PK/p-AurA biomarker and PK/tumour size model structures. Following this tool compound evaluation, the PK and PK/biomarker relationship for LY3295668 was subsequently assessed and, once adjusted for PK and potency, its tumour shrinkage was predicted using the Compound X PK/tumour size model.

Results: For Compound X, a one compartment PK model and simple Emax models successfully described its oral disposition and relationships between PK and p-AurA inhibition, and PK and tumour growth inhibition. The same PK and PK/p-AurA biomarker model structures also sufficiently described the data obtained for LY3295668, with a difference in in vivo potency of approximately 2-fold. Notably, Compound X-mediated tumour shrinkage exhibited a steep PK/PD relationship with an estimated IC50 which was equivalent to the PK/p-AurA IC90. This comparative analysis indicates selective Aurora A inhibition-mediated tumour shrinkage is driven by extended time at or above 90% target inhibition. Using the PK/PD relationships established for Compound X, and adjusting for PK and potency, the tumour shrinkage mediated by LY3295668 was successfully predicted across a range of doses.

Conclusion: The quantitative pharmacology of selective Aurora A inhibition was investigated using a tool compound (Compound X) and successfully predicted for subsequent compounds, of which LY3295668 was advanced to clinical evaluation. This PK/PD evaluation of selective Aurora A inhibitors during a drug discovery programme enabled informed design and selection of compounds with greatest potential for clinical efficacy.

I-29: *Nadia Terranova* The CICIL tool: a Java-based user-friendly application for the analysis of individual tumor size lesion dynamics

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Objectives: Clinical models of tumor dynamics generally omit information on individual target lesions (iTLs), and use the total tumor size (TS) as a continuous variable to model the tumor time-course. However, differences in lesion dynamics might be predictive of tumor progression. To exploit this information, we have integrated knowledge from signal processing and machine learning into a novel and flexible approach for the non-parametric analysis of iTLs [1, 2]. We called this new methodology ClassIfication Clustering of Individual Lesions (CICIL). In this work, we present the CICIL tool, a Java-based cross-platform implementation of the CICIL methodology, recently made available to the scientific community [2].

Methods: The CICIL methodology relies on the classification of iTLs based on functional and anatomical criteria, and it consists on a workflow accommodating the assessment of similarity among dynamics of lesions classified as belonging to the same anatomical site (intra-class analysis) or to different sites (inter-class analysis). Such degree of similarity is assessed through cross-correlation measures, and the interpretation of the results is facilitated by the k-means clustering [2].

To enable the efficient execution of this methodology and to assist the interpretation and visualization of each individual step in the workflow, CICIL has also been implemented in a user-friendly Java-based framework [2]. The CICIL tool, through its functional and interactive graphical user interface (GUI), enables a user to seamlessly create new projects, import and manipulate datasets, and run the CICIL workflow to obtain a series of informative graphical plots and well-structured statistical summaries. Moreover, the tool is modular and flexible as it provides a high degree of customization for its core components. For example, the iTLs classification can be defined by using standard terms automatically extracted from the dataset through a text-mining algorithm or a set of keywords directly defined by the user. Similarly, the user can select the desired results that she/he wants to export and automatically generate customized reports directly through the GUI.

Results: The CICIL tool's executable (JAR file) is publicly available as Supplementary Material of Terranova et al. [2] along with a use case based on a mock dataset. The tool can be executed on operating systems which contain a version of the Java Runtime Environment, minimum v1.7, and has been tested in Windows 7 and 8. System requirements and application features are described in the respective user guide embedded in the tool.

Conclusions: The CICIL tool constitutes a user-friendly and flexible platform enabling a straightforward execution of the CICIL methodology to efficiently analyze and understand large-scale datasets prior to modeling. The results can then guide the modeler in determining whether a total TS evaluation might reasonably predict tumor lesion behavior, or potential differences in responses, within or across tumor site classes, should be taken into account for a particular case study and for the questions to be addressed.

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I-30: *Adrien Tessier* Population pharmacokinetics in adults and model-based extrapolation and dose selection in the paediatric DMD population for drug S48168/ARM210

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Objectives: S48168/ARM210 is proposed orally for the treatment of Duchenne Muscular Dystrophy (DMD) in children from 5 years old. A phase I program was performed in adults and consisted of a single (SAD) and multiple ascending dose (MAD) study, a formulation bridging study and a DDI study. A model-based strategy was proposed to predict the S48168/ARM210 PK in children and support dose selection for studies in the DMD population. With this purpose in mind, a population PK model was developed using data in adults and was allometrically scaled to children.

Methods: S48168/ARM210 plasma concentrations in 61 adult male healthy volunteers (HV, all Caucasian and CYP2C8 extensive metabolizers) from the SAD, MAD and DDI studies were used to develop the adult model for doses from 20 to 240 mg. Plasma concentrations in 11 subjects at 20 mg from the formulation bridging study were used externally to assess the formulation effect (a previous NCA analysis showed a relative bioavailability equal to 1).

Model estimation was performed using Monolix version 2016R1 software and SAEM algorithm.

The effect of demographic covariates such as body weight was not tested. Allometric functions on total body weight were applied without test on apparent distribution and elimination parameters assuming pre-defined fixed exponent of 3/4 for clearance and 1 for volume parameters [1]. Because the drug is proposed in children from 5 years old, metabolism pathways are assumed mature and no maturation function was used.

The effect of Gemfibrozil (a strong CYP2C8 inhibitor) co-administration in the DDI study on S48168/ARM210 PK was investigated as a categorical covariate on the relative bioavailability (F) and CL/F.

Using published body weights according to age [2], doses selection for the study in children was performed. Using the scaled model, PK profiles were simulated to derive Cmax and AUC at steady-state. Doses were selected for different weight-bands to achieve in children the same exposures as observed in adults from the MAD study for the two highest dose levels tested and that were safe (60 and 120 mg).

Results: The complex and highly variable absorption was best described by a sequential first- and zero-order absorption process with a lag-time and high IIV and IOV on some parameters. The disposition was best described by a 2-compartment model with a linear elimination and low IIV and IOV. The residual error was modeled using a combined error model.

A dose effect was significant on F and the duration of the zero-order process with three and two doses categories respectively. The effect of co-administration with Gemfibrozil was significant on CL/F and associated to a decrease by 37% of the typical value. Allometric functions based on total body weight were then included with fixed exponent (on V1/F, V2/F, Q/F and CL/F).

Model evaluation showed that the final model described adequately the drug plasma PK in adult HV. Visual Predictive Checks and Posterior Predictive Checks of derived parameters (Cmax and AUC) showed that the model is qualified to simulate new data.

Using simulations performed with the scaled PK model in children, 6 weight-bands (from 15 to more than 55 kg) were identified in order to keep the exposure in children within the range of exposures found in adults. One dose was proposed for each weight-band, the highest corresponding to the dose given in adults. Thus two set of doses were proposed corresponding to the two highest and safe dose levels tested in adults in the MAD study.

Conclusions:

A population PK model developed through a combined analysis can describe the pharmacokinetics of S48168/ARM210 in plasma for adult male HV. This model was qualified through different metrics. Scaling allometrically the model to fit known weight classes for children can then be used to pick potential doses to match resulting safe exposure levels in children to those previous established in healthy adult males. Both Cmax and AUC parameters can be used with one of those parameters dominating the dosage selection.

The scaled population PK model will be used during the first study in the DMD population in order to support the dose adaptation during the dose escalation process.

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I-31: *Mita Thapar* Population pharmacokinetic and exposure-lymphocyte analysis of FTY720 (Fingolimod/Gilenya) in pediatric patients with Multiple Sclerosis

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Objectives:

The objectives of the present analysis were:

- to develop a linear mixed effects PK model to describe the FTY720-P concentrations at steady-state in the MS pediatric patient population using data from Study CFTY720D2311 (D2311).
- to assess by performing a visual predictive check (VPC) whether the previously developed adult FTY720-P exposure-lymphocyte model described the pediatric lymphocyte data from study D2311 and to re-estimate the parameters of the exposure-lymphocyte model using a combined dataset of adult and pediatric patient data.

Methods:

Population PK model

- A linear mixed effect model was developed to describe the FTY720-P concentrations at steady-state in the pediatric MS patients using data from Study D2311 alone;
- Age, weight and dose group were investigated (both as time-varying and time-invariant) covariates in the present analysis;
- The final population PK model was evaluated by performing a prediction corrected (pc) VPC.

Exposure-lymphocyte count model

- An exploratory pc-VPC was performed to assess whether a previously developed adult exposure-lymphocyte model described the pediatric lymphocyte data from Study D2311;
- The parameters of the exposure-lymphocyte model were re-estimated using a combined dataset from adult and pediatric patients to determine which parameters were different between the adult and pediatric populations. A binary pediatric/adult covariate was added on the model parameters, baseline, IC50 and Imax to assess the potential difference between adult and pediatric patients;
- The final exposure-lymphocyte count model was evaluated by performing a pc-VPC.

NONMEM® program version VII level 3.0 was used for all analyses using PDx-Pop (Version 5.2) as an interface.

Results:

Population PK model

- Following administration of 0.5 mg per day of FTY720 in a pediatric population, the typical steady-state FTY720-P concentration for a body weight of 70 kg (0.978 ng/mL) was within the 90% CI

around the median of the adult target FTY720-P steady-state concentration and higher than the 65% relative bound (0.878 ng/mL) of the adult target FTY720-P steady-state concentration level.
- The steady-state FTY720-P concentrations were dose proportional following 0.25 and 0.50 mg capsule formulation of FTY720 in the pediatric population.
- The steady-state FTY720-P concentrations decreased slightly with increasing body weight. The decrease in concentration was non-linear. An increase of 10 kg weight from 20 to 30 kg and from 70 to 80 kg resulted in a 15.2% and a 5.3% decrease in FTY720-P concentrations, respectively.

Exposure-lymphocyte count model

- The FTY720-P exposure-lymphocyte relationship in adults is an I_{max} model relating the estimated FTY720-P concentrations at steady state to the absolute lymphocyte count.
- The baseline lymphocyte count was estimated to be 17.2% higher in pediatric patients compared to the adult population. Both I_{max} and IC_{50} were comparable between pediatric and adult populations with I_{max} 6% lower (95% CI: 8% higher to 20% lower) and IC_{50} 12% lower (95% CI: 4% higher to 66% lower) in pediatric versus adult patients.
- The baseline lymphocyte count was slightly higher for higher baseline weights. A 10-kg increase in weight (from 70 to 80 kg) resulted in only a 2% increase in lymphocyte count.

Conclusions:

Overall, the FTY720-P exposure was considered similar between adult and pediatric patients. The exposure-lymphocyte count analysis suggested that there is no evidence of a difference in the exposure-response relationship between adult and pediatric patients once the difference in baseline is taken into account.

I-32: *Pauline Themans* Prediction of meropenem systemic and infection site exposure and open-loop control strategy for optimal drug dosing: a PBPK approach

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Objectives: To develop a reduced physiologically-based pharmacokinetic (PBPK) model using a retrograde approach based on a previously developed compartmental pharmacokinetic (PK) model in patients with severe nosocomial pneumonia and to propose an approach for individualized drug dosing. A control strategy was designed to achieve and maintain plasma and epithelial lining fluid (ELF) concentrations at target levels.

Methods: Steady-state PK data were obtained from 60 adult patients diagnosed with severe lung infection [1]. They included rich plasma and sparse ELF samples. Previously, a two-compartment model with an additional compartment for the site of effect (ELF) was successfully fitted to the data [6]. A reduced PBPK model was developed using NONMEM version 7.3. Model qualification was based on successful numerical convergence, adequate precision in parameter estimates (as assessed by bootstraps), acceptable goodness of fit plots with no indication of bias, and acceptable performance of visual predictive checks (VPCs). External validation was performed by fitting the model to external independent data. Data from two previously published studies on meropenem were used for external validation [3], [2]. Graphical analysis was performed using R version 3.0.2 and MATLAB 2014b.

The analytical expression of the asymptotic response (i.e. when time goes to infinity) was determined and used to derive a closed-form formula designed to estimate the effective dosing regimen, given the patient's characteristics and the target minimal concentration (open-loop control method). The system asymptotic response corresponds to the pharmacokinetic steady-state. This method was studied and validated with MATLAB 2014b.

Results: A reduced PBPK model with six compartments (arterial and venous pools, lungs, liver, kidneys and rest of the body) provided an adequate fit to the data. The model was successfully qualified internally and externally as described above. Numerical simulations showed that the system output trajectory converges exponentially towards the asymptotic response, so that the asymptotic response (steady-state) is a good approximation of the actual response after few dosing intervals. Numerical simulations were performed to produce pharmacokinetic profiles using the open-loop dosing approach. Simulations of concentrations in ELF for average virtual patient receiving the recommended maintenance dose (1.47 grams) for the susceptibility breakpoint of 2 mg/L show that 50% of the simulated patients are above the target concentration for 100% of the dosing interval; 75% reach the target concentration for at least 80% of the dosing interval (this value is an approximation, as exact value changes at each iteration).

Conclusions: A dosing strategy based on a formula in a closed-form was proposed which displayed acceptable and reliable results. The established formula can be readily generalised to any n-compartment model.

However, its open-loop nature does not take into account unexplained interindividual variability and only provides a result for the average patient. The proposed PBPK model can alternatively be integrated in other existing tools enabling dosing optimization such as Maximum A posteriori Bayesian estimations [4], [5].

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I-33: *Tjokosela Tikiso* TB/HIV co-treatment with superboosted lopinavir lowers abacavir concentrations in children

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Objectives: Co-treatment of HIV and tuberculosis in infants and young children is unavoidable in much of Africa, increasing risks for drug-drug interactions (1). More data is needed to characterise drug interactions to better manage children of various ages. No data is available on the pharmacokinetics and efficacy of abacavir when co-administered with rifampicin-based tuberculosis treatment and super-boosted lopinavir (LPV/r plus additional ritonavir). Our objective is to compare pharmacokinetics of abacavir during treatment with standard doses of LPV/r vs. anti-TB treatment and super-boosted lopinavir.

Methods: 87 TB/HIV-infected South African children (median age: 2.8, range 0.25-6 years; weight: 9.4, 4-16 kg) were sampled on 3 separate visits: (a) after at least 2 weeks on TB treatment and super-boosted lopinavir during the intensive phase and (b) at the end of the continuation phase of TB treatment; and (c) one month after TB treatment completion on standard doses of LPV/r dose without additional ritonavir. Abacavir twice-daily was co-administered throughout. All drugs were dosed according to the South African weight-band dosing recommendations. At each visit, blood samples were collected immediately before dosing and 1, 2, 4, 6, 8, and 10 hours thereafter. NONMEM 7.3 with FOCE-I was used to develop a population pharmacokinetic model. PsN, Pirana and Xpose were used to facilitate modelling and model diagnostics (2). Allometric scaling (3) was used to account for the effect of body size, using different predictors such as fat-free mass (FFM), fat mass and total weight. The effect of maturation (4) on clearance was tested as a potential covariate. Data below the limit of quantification was imputed with half the value of low limit of quantification, and only the first values in a series was retained in the analysis, as outlined in the method M6 by Beal et al (5).

Results: Abacavir pharmacokinetics was best described by a two-compartment model with first-order elimination and transit compartment absorption. Allometric scaling was used to adjust for the effect of body size, after which maturation could be identified: clearance was predicted to reach half its mature value at around 2 months after birth and to be fully mature by around 2 years of age. The typical clearance in a 9-kg child co-treated with normal dose LPV/r is estimated at 8.8 L/h. During co-administration of TB treatment with lopinavir super-boosting, a 38% decrease in bioavailability was found. Finally, the trough concentrations observed just before the morning dose were higher than the extrapolated values predicted 12 h after a morning dose, and this was best explained by including a 24% reduction in clearance overnight.

Conclusions: The proposed model successfully characterised the PK of abacavir, including the effect of body weight and age**.** Abacavir exposure was significantly decreased by concomitant administration of rifampicin and super-boosted lopinavir. Larger trough concentrations were observed in the morning, possibly indicating circadian variation in the pharmacokinetics. Although 67 (82%) children were virologically suppressed at the end of TB treatment compared to 6 (6%) at study entry, further investigation should address whether dosing adjustments are necessary to counteract the effect of the drug-drug interaction.

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I-34: *Tom Haber* DiffMEM: an open-source package for high-performance pharmacometric model estimation

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Introduction: DiffMEM is an open-source software package, freely available on Bitbucket[1], for rapid optimization of non-linear mixed effect models using ordinary and partial differential equations (ODE/PDE). During parameter estimation, these ODE/PDE's are frequently integrated numerically since parameters change between individuals and across iterations. This can be computationally expensive, resulting in long runtimes for model fitting. Consequently, this can seriously limit building, testing and using such models. However, through heavy use of parallelism, extensive low-level optimizations and algorithmic innovation [3], DiffMEM is able to rapidly fit such complex models. Duty-cycles are shortened while building a model, adaptive/optimal trial design is enabled, and model validation becomes possible, since these typically require a lot of simulation-estimation steps. DiffMEM is under active development with interfaces to R and Python, and an exciting innovation is the concept of model fitting as a web-service which completely decouples the software/hardware configuration from the fitting process.

Objectives:

- Examine estimation properties of the SAEM routines implemented in DiffMEM and compare with several other methods and implementations based on the methodology from Plan et al. [2]
- Compare the performance between DiffMEM and NONMEM in several real-life use-cases

Methods: Plan et al. [2] considered a sigmoid Emax model with one hundred individuals with observations at four doses (rich design) and two doses (sparse design) to study nine approaches for ML estimation. One hundred simulated datasets were generated for each of eight scenarios. The SAEM estimation routine in DiffMEM is tested on the same datasets to compare its results to the other nine approaches.

DiffMEM was used for the parameter estimation on the ODE based PK/PD models from real-life use-cases by Dunne et al. [4] and de Winter et al. [5]. The estimation was performed on the original models without alterations. The former model consists of two-compartment PK model and turn-over PD model. Dunne et al. [4] used a sequential estimation method: PK parameters are estimated in a first step and are subsequently fixed while fitting PD parameters in the second step. In our comparison, we will only focus on this second step. The latter is a population PK model based on a turn-over model for HbA1c consisting of 1347 type-2 diabetic patients. In both settings, we compare performance of DiffMEM with parallel NONMEM.

Results: The SAEM routine in DiffMEM consistently produces comparable results to other SAEM approaches investigated by Plan et al. [2]. With the real-life use-cases, DiffMEM is able to produce similar results, but runtime is much lower: model fitting using parallel NONMEM with 24 cores takes respectively 3 hours and 8 hours whereas using DiffMEM the runtime is reduced to 10 and 20 minutes.

Conclusions: The study suggests that DiffMEM is a viable open-source alternative for parameter estimation of non-linear mixed effect models while being an order of magnitude faster in delivering results. The open-source nature allows for relatively easy extension to novel types of models.

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I-35: *Elena Tosca* In vitro-in vivo correlation (IVIVC) population modeling for the in silico bioequivalence of a long-acting release formulation of Progesterone.

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Objectives: Health authorities carefully evaluate any change in the batch manufacturing process of a drug before and after regulatory approval. In absence of an adequate *in vitro-in vivo* correlation (level A IVIVC) (1) an *in vivo* bioequivalence study is frequently required (2), increasing drug development costs and time to market. This work proposes a population modeling approach to establish a level A IVIVC between the *in vitro* release of two batches of Progesterone vaginal rings (PVRs), a dosage form designed for the continuous delivery *in vivo*, and the corresponding serum profiles observed during clinical studies. Estimates of the expected *in vivo* relative bioavailability of two tested batches can also be obtained from the model here proposed.

Methods: Experimental methods: *In vitro* data included time courses (24-408h) of the amount of released Progesterone for 2 batches of rings (reference batch A and test batch B) manufactured by Italfarmaco S.p.A.. Data at 4 different dose levels (125, 375, 750, 1500 mg) were available for batch A, while only 375 mg data were available for batch B. *In vivo* Progesterone serum level profiles were collected in clinical studies performed on batch A (54 subjects); for each subject, the total amount of Progesterone (P) released within the experimental period was also measured. Model-based approach: Development of: (i) a model describing the *in vitro* release profiles of P at each dose level (Pvitro Model); (ii) an *in vivo* release model accounting for the limited solubility of P in the finite volume of vaginal fluid (Pvivo Model); (iii) a global population IVIVC Progesterone ring (IVIVC P-ring) model including the Pvivo Model, able to predict, at each dose level, the *in vivo* serum P concentration profiles.

Results: For both batches and for all the doses, time profiles of the accumulated Pvitro release appeared well described by the sum of a biexponential model and an immediate release in the medium (a common behaviour for this type of dosage form). For each dose level, different rings (6-12) from the same batch were tested; however, a unique curve was estimated using a pooled data approach because the release profiles were so close to consider negligible their inter-ring variability. The Pvivo release Model follows the Pvitro one apart from the addition of a dose dependent inhibition function acting on the biexponential release. Then, the Pvivo release enters a two-compartment PK model with first-order absorption rates that yields the serum P concentration (IVIVC P-ring model). Fixing the Pvitro parameters to the values obtained from the *in vitro* data, *in vivo* model parameters were estimated in NONMEM performing a simultaneous fitting on all the dose levels of batch A. As recommended by the regulatory guideline (1), the predictive performance was evaluated internally assessing the absolute percent prediction errors (%PE) for AUC(0-t) of P serum concentrations. For AUC(0-408h), %PE was <2% for each dose, remaining always <7% at all sampling times. Model external predictability was assessed identifying the IVIVC P-ring model leaving out the 375 mg data that were considered as external dataset. Visual predictive check plots (500 simulated individuals) were used to assess the model predictive performance when compared with the external 375 mg dataset. For the average AUC(0-t), %PE was <10% for sampling times after 264h and <3% at the end of the experiment. In addition to the standard "level A IVIVC" procedure, the population approach here developed allows to performe simulation studies providing estimates of the relative bioavailability *in vivo*

(F=AUCtest/AUCref) of any new batch tested *in* vitro in comparison to a reference one. For example, considering here the 375 mg dose, 500 serum P profiles were generated with the IVIVC P-ring model previously identified on batch A; then, other 500 serum P profiles were obtained for batch B using the same model parameters apart the *in vitro* parameters that were re-estimated from its *in vitro* release dataset. From the AUC values of the two populations, the *in vivo* relative bioavailability was directly obtained, F=0.913 with 90%CI = [0.878, 0.948].

Conclusions: In this work, a level A IVIVC model for PVRs was developed and its internal and external predictability was evaluated. In addition, using a population approach, the IVIVC P-ring model resulted a useful tool for the assessment of the *in vivo* bioequivalence from *in vitro* studies performed with a new batch.

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I-36: *Kota Toshimoto* Application of virtual clinical studies to predict the effect of inter-individual differences on the drug/metabolites exposures in the blood and target organs leading to different pharmacological and toxicological effect

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Objectives:

This study shows the potential of virtual clinical study (VCS) to predict the effect of inter-individual differences on drug or metabolite exposures in blood and target organs leading to pharmacological and toxicological effects [1]. VCS is computational simulation with physiologically-based pharmacokinetic (PBPK), pharmacodynamic, and toxicodynamic models to generate virtual patients with the variability of physiological and pharmacokinetic parameters based on genetic polymorphism, ethnic differences, and inter- and intra-individual variability [2, 3]. Irinotecan is intravenously administered for various cancer treatment. SN-38 is an active metabolite of irinotecan and causes serious side effects including neutropenia and diarrhea. UGT1A1 polymorphism increases risk of the side effects because of higher SN-38 exposure due to decreased UGT1A1 metabolic activity, and similar results have been reported in different clinical studies [4]. Except for UGT1A1, there has been no clear association between the side effects of irinotecan and the effect of genetic polymorphism of other transporters including organic anion transporting polypeptide (OATP) 1B1, multiple drug resistance (MDR) 1, breast cancer resistance protein (BCRP), and multidrug resistance-associated protein (MRP) 2.

Methods:

Because there were many unknown parameters in the PBPK model, it was difficult to determine appropriate initial values for unknown parameters. Thus, conventional nonlinear least squares methods such as the Gauss–Newton method and Levenberg–Marquardt method could not be applied. To overcome this problem, Cluster Newton method (CNM) was newly introduced to optimize unknown parameters of PBPK model [7]. In CNM, multiple sets of initial values of parameters were generated at random from a certain range for each unknown parameter. Then, linear approximations of projection from parameters to objective function were used to determine the next iterations from initial sets. To perform VCS, not only the inter-individual variability for each physiological and physicochemical parameters of the PBPK model but also the genetic polymorphisms of enzymes and transporters were considered. A virtual patient was generated by performing Monte Carlo simulation given a frequency distribution (average and coefficient of variation) for each parameter and the activity ratio and the allele frequency for each genetic polymorphism obtained from experiments in vitro and in vivo [8-12]. VCS was performed to find whether the PBPK model that reproduced a blood concentration–time profile, could reproduce the results of a previously reported clinical study. The patients with high unbound plasma AUC were assumed to have neutropenia and those with high unbound enterocyte AUC were assumed to have diarrhea.

Results:

Using CNM, thePBPK model with approximately 30 sets of parameters could give good reproduction of the pharmacokinetics of irinotecan and its metabolites. The computational time for CNM optimization with the initial 10,000 sets of parameters was about 15 min using a workstation (CPU: Xeon E5-2640 v3 ´2; OS: CentOS 6.7 64 bit; RAM: 32 GB). This result shows that CNM is a powerful algorithm by which to find

multiple sets of parameters for PBPK models quickly. The VCS confirmed that the genetic polymorphisms of UGT1A1 affected the SN-38 plasma concentration, and was associated with neutropenia. The VCS also indicated that "biliary index (= $AUC_{(irinotecan)}$ ´ $AUC_{(SN-38)}$ / $AUC_{(SN-38\ glucuronide)}$), [13]" is a better biomarker of diarrhea than the UGT1A1 polymorphism.

Conclusions:

The multiple sets of PBPK model parameters could reproduce the effects of genetic polymorphisms of UGT1A1 on the plasma concentration of SN-38 and side effects such as neutropenia and diarrhea using a VCS approach. To optimize the numerous biochemical parameters of irinotecan and its metabolites in the PBPK model, a CNM parameter optimization algorithm was introduced. The current VCS confirmed the importance of the biliary index as a better biomarker of irinotecan-induced diarrhea compared with only UGT1A1 polymorphism. In this study, VCS was performed to evaluate whether reported clinical studies could be reproduced by the PBPK model,in a "retrospective" approach. To examine the potential of VCS to apply it to the "prospective" prediction, VCS for another anti-cancer drug is on-going prior to the results of clinical study published.

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I-37: *Pauline Traynard* New library of time-to-event (TTE) models for the MonolixSuite and application to two experimental data sets

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Objectives: Time-to-event data are often analyzed using non-parametric or semi-parametric (e.g Cox models) approaches. These approaches are simple but also have limitations. Parametric approaches offer a powerful alternative, which enables the use of frailty, mixture or even joint PK-TTE or PD-TTE models. They also allow to perform simulations for new treatments, or new populations with different covariate distributions. We illustrate the use of parametric models using the MonolixSuite, on two typical data sets: a TTE data set of survival in lung cancer patients [1], and a PD-TTE data set of serum bilirubin and liver transplant in primary biliary cirrhosis patients [2]. To simplify the testing of several models, a library of typical TTE models has been implemented for the MonolixSuite.

Methods: The developed library of TTE models contains the most common parametric TTE models, i.e exponential, Weibull, log-logistic, uniform, Gompertz, gamma and generalized gamma models, with or without delay and for single or repeated events. The library is used to find appropriate models for two data sets: survival in lung cancer and liver transplant.

Results: We first use the Mlxplore application from the MonolixSuite to perform a sensitivity analysis of the influence of each parameter. A summary is presented to guide the users in their choice of an appropriate model for their data. The lung cancer data set is then stepwise modeled. All models from the library are tested and compared using the likelihood ratio test and a visual assessment of the Visual Predictive Check for time-to-event data implemented in Monolix. The Gompertz model shows the best agreement with the data. Available covariates are then tested using a backward strategy. Sex and the ECOG performance score appear as significant covariates. The model is then used to perform a variety of simulations and predict the survival in cohorts with particular distributions of covariates. The uncertainty of the predicted survival is also assessed with simulation replicates. For the PD-TTE data set on liver transplant, a continuous model is first developed for the serum bilirubin. A joint PD-TTE model is then implemented, in which the bilirubin concentration impacts the hazard of transplantation in a proportional way. The model shows reliable parameter estimation and a good agreement with the data.

Conclusion: The choice of a parametric model for time-to-event data is more complicated than for continuous outcomes because no direct model representation exists. The provided visual summary of the typical survival functions corresponding to typical time-to-event models is a useful guide for modelers. Using this guide and the diagnostic plots provided by Monolix, appropriate parametric models can be found for both experimental data sets. The MonolixSuite and the new TTE library allow an efficient modeling and diagnostic of parametric models for TTE or joint continuous-TTE data. The TTE model library has been made available in the 2018R1 MonolixSuite release.

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I-38: *Iñaki F. Trocóniz* An immune quantitative framework for Hepatitis B viral infection

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Objectives: Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV) that affects the liver, a known organ for its capability to develop tolerogenic immune responses [1]. After infection in adults, approximately 95% of the subjects developed an acute infection (AHB) and are capable to mount an adequate immune response that leads to the subsequent resolution of the infection within 1 – 3 months [2]. However, the other 5% of patients experience a more tolerogenic immune response leading to chronicity of the infection. The CHB patients tend to develop complications such as cirrhosis and hepatocellular carcinoma, and finally, death.

A topological model representing the interaction between the key elements of the HBV and the immune system –in terms of location, causality and nature of the relationship- was recently developed by our group [3]. This representation provides a comprehensive overview of the system, but it does not account for the magnitude of the response nor the temporality. Consequently, the objective of this work is to build a multiscale quantitative system pharmacology (QSP) model able to characterize the immune response against HBV.

Methods: The topological model was used as the basis for the QSP model in terms of entities and processes. Ordinary differential equations (ODE) describing the temporal changes of the identified components were implemented in Matlab/Simbiology R2017a using zero-, first-, and second-order processes. Inhibitory and stimulatory effects were integrated using standard pharmacodynamic models. Model parameters were obtained directly from the literature or computed from human in vivo or in vitro studies where the interactions between components had been quantitatively characterized. When needed, data were digitalized using WebPlotDigitalizer v3.8 and analyzed in R v3.3.2 and NONMEM7.3. Simulations were confronted with data from AHB patients obtained from the literature [4-7]. Finally, a sensitivity analysis was performed varying the different model parameters +/- 10% and exploring its impact on clinically relevant markers such as time to cure (HBVDNA < 2000 IU/mL) and maximal HBVDNA or ALT levels.

Results: An ODE-based model (35 equations, 86 parameters) representing the temporal evolution of the HBV-related immune response across 3 different compartments - liver, plasma and lymph node- has been successfully developed. The framework included the key element from the viral dynamics together with the innate, adaptive, and regulatory immune response identified from the topological model from a molecular (e.g cytokines) to cellular (lymphocytes) level.

The model was able to reproduce the HBV-related immune response in terms of chronology and plausibility of component levels during an acute process. Simulations highlight the limited contribution of the innate response to the control of the disease, but its central role triggering the adaptive response, together with the role of the immunoregulatory system in the establisment of a chronic infection. Indeed, changes of only

10% in model parameters controlling the tolerogenic response were sufficient to switch from an acute to a chronic viral response. The sensitivity analysis revealed that the cytotoxic lymphocytes proliferation rate constant, the cytokine levels, and the degradation of the HBV had the larger impact on maximum achieved levels of HBVDNA in plasma, while the duration of the acute disease was meanly controlled by parameters related to the viral dynamics (infectivity capability and virus degradation rate).

Conclusions: A multiscale QSP model characterising the HBV immune-related response has been developed. The model developed provides an adequate quantitative framework to (i) understand the role and contribution of the innate, cellular and humoral immune response to the viral erradication, and (ii) explore the mechanism of action of different agents and their effects in terms of efficacy and safety.

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I-39: *Denise Tuerk* Physiologically-based pharmacokinetic modeling of gemfibrozil drug-drug interactions with the CYP2C8 victim drugs repaglinide and pioglitazone

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Objectives: Physiologically-based pharmacokinetic (PBPK) modeling is a valuable tool to describe and predict the extent of drug-drug interactions (DDIs) and to investigate the influence of perpetrator drugs on the pharmacokinetics (PK) of victim drugs. The lipid-lowering drug gemfibrozil [1] is recommended by the U.S. Food and Drug Administration (FDA) as a strong CYP2C8 inhibitor for the application in DDI studies [2]. The gemfibrozil phase-II metabolite gemfibrozil 1-O-β-glucuronide is the main cause of this strong inhibition, inactivating CYP2C8 in a mechanism-based manner [3]. Co-administration of gemfibrozil with the CYP2C8 victim drugs repaglinide and pioglitazone leads to 8.1-fold [4] and 3.4-fold [5] increases in the area under the curve (AUC) of repaglinide and pioglitazone, respectively. The objectives of this study were to develop a PBPK model of gemfibrozil and to predict the DDIs of gemfibrozil with repaglinide and pioglitazone.

Methods: A whole-body PBPK model of gemfibrozil was established with PK-Sim® modeling software (Version 7.2.0) [6,7]. Drug-dependent parameters and plasma concentration-time profiles of 23 clinical studies of gemfibrozil (oral application, single and multiple dosing, dosing range 30-900 mg) were taken from literature. Optimization of parameters that could not be informed from literature was accomplished using the studies of the internal data set, followed by evaluation of the predictive performance of the model by comparison of predicted and observed plasma profiles of the studies belonging to the external data set. Parameters describing the competitive inhibition of CYP2C8 by gemfibrozil and the mechanism-based inhibition of CYP2C8 by its glucuronide [8,3], as well as the competitive inhibition of OATP1B1 by both [9], were added to the gemfibrozil model. Lastly, the gemfibrozil model was coupled to previously developed models of repaglinide and pioglitazone [10].

Results: To mechanistically describe the strong inhibition of CYP2C8 by gemfibrozil, a parent-metabolite model was established. The gemfibrozil model includes an active uptake into hepatocytes, metabolism by UGT2B7 to form gemfibrozil 1-O-β-glucuronide and glomerular filtration. The gemfibrozil 1-O-β-glucuronide model applies an active uptake into hepatocytes via OATP1B1, transport via MRP3, a biliary clearance and glomerular filtration. The quality of the gemfibrozil model can be described by AUC ratios (AUC predicted / AUC observed), which show a low geometric mean fold absolute deviation (GMFE) of 1.15 (range 1.02-1.39, n=18). Application of the newly developed gemfibrozil model for DDI prediction shows that the plasma concentration-time profiles of the victim drugs (repaglinide and pioglitazone) are well predicted in case of gemfibrozil co-administration. Predicted vs. observed DDI AUC ratios (AUC DDI / AUC control) show a GMFE of 1.59 (range 1.07-3.27, n=13) for the gemfibrozil-repaglinide DDI and of 1.06 (range 1.03-1.08, n=2) for the gemfibrozil-pioglitazone DDI, indicating an adequate predictive performance of the PBPK models.

Conclusions: A PBPK model of the CYP2C8 inhibitor gemfibrozil including its metabolite gemfibrozil 1-O-β-glucuronide has been successfully established. The model precisely describes plasma concentration-time profiles of gemfibrozil over a wide dosing range. Furthermore, the model accurately predicts different co-administration scenarios of gemfibrozil with repaglinide and of gemfibrozil with pioglitazone and is a useful tool to investigate the DDI potential of CYP2C8 victim drugs or to inform the design of clinical DDI studies.

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I-40: *Sami Ullah* Population pharmacokinetic analysis of piperacillin in acute haemorrhagic stroke patients - a cerebral microdialysis study

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Objectives:

Piperacillin is an extended-spectrum penicillin antibiotic with excellent activity against Gram-positive and -negative bacteria and is thus frequently used as an empirical therapy in various nosocomial infections. In a microdialysis study conducted in septic shock patients, free concentrations in the interstitial fluid (ISF) of skeletal muscle and subcutaneous adipose tissues were 5-10 times lower than corresponding unbound plasma concentrations with mean penetration ($AUC_{ISF}/AUC_{unbound\ plasma)}$ values of 0.19 and 0.10 respectively (1). However, less data is available regarding effective concentrations of piperacillin reached in the brain of severely ill patients.

The aim of this evaluation was to assess piperacillin penetration into the ISF of the brain in critically ill patients by use of a population pharmacokinetic model.

Methods:

Data were available from 10 comatose patients with acute haemorrhagic stroke (median age and body weight of 48 [range 32-72] years and 75 [60-95] kg) being treated for nosocomial pneumonia in an ICU setting. After getting approval from ethics committee and informed consent from the patients, each patient was administered a standard dose of 4 g of piperacillin in combination with 0.5 g tazobactam every eight hours by a 30-minute infusion. Microdialysis samples from interstitial space fluid of human brain parenchyma, representing unbound ISF concentrations, were collected in one-hour intervals after single dose and at steady state. Concentrations were quantified by reversed-phase high-performance liquid chromatography. The lower limit of quantification was 0.05 mg/L. Population pharmacokinetic modeling and covariate analysis were performed using NONMEM 7.4.1 software. Because plasma samples were not available, a published two compartment plasma pharmacokinetic model of piperacillin was selected to drive brain concentrations (2).

Results:

One additional compartment was added to describe brain microdialysis data. To account for an observed delay in the initial rise of concentrations in the brain, a lag time and a transit compartment were introduced. The model was parameterized in terms of inter-compartmental clearance between plasma and brain (Qb = 1.54 L/h), apparent volume of distribution of brain (Vb = 5.28 L), absorption lag (ALAG = 3.01 h) and a transfer rate in the transit compartment (Ktr = 0.092 h^{-1}). Inter-individual variability [CV%] was found to be 50.5%, 30.3% and 83.4% on Qb, absorption lag and Ktr respectively. At steady state, Monte Carlo simulations suggested that median AUC_{0-24} ratio ($AUC_{ISF}/AUC_{unbound\ plasma}$) was 0.059 (95% prediction interval 0.014-0.25). Plasma protein binding of piperacillin was assumed to be 30% in our analysis. No meaningful covariates of pharmacokinetic parameters were identified.

Conclusions:

The empirical model was able to describe the data well. The observed delay for piperacillin to reach the brain advocates for the earliest possible administration of piperacillin in infections involving the CNS.

Further evaluations are needed to ascertain whether the current dosing regimen of piperacillin is sufficient to treat the nosocomial CNS infections in patients with acute brain injuries.

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I-41: *Chakradhara Rao Satyanarayana Uppugunduri* Population pharmacokinetic model for individualized busulfan dosing in children: Annexation to the existing vast list of PopPK models for performance evaluation

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Background and Objectives:

Busulfan (Bu) dosing in children has been improved recently with the development of personalized dosing algorithms based on population pharmacokinetic studies (PopPK). However, performance of these models is not optimal but has significantly improved targeted therapy.[1, 2] Few PopPK models evaluated the impact of GSTA1 genetic variants on inter-individual variability (IIV) of Bu clearance (CL). Since cumulative AUC of Bu is linked to outcomes,[3] inter-occasional variability (IOV) in its CL determines the overall cumulative exposure. It is also well known that Bu conjugation is catalyzed predominantly by GSTA1 enzyme. No model has evaluated the effect of covariates such as hematocrit and genetic variants in GSTA1 on IOV in Bu CL. The objective of this study is to develop a PopPK model for intravenous Bu in children and to evaluate dynamic and static covariates such as anthropometric, clinical (hematocrit) characteristics and genetic variants (GSTA1 functional haplotypes) that might explain IIV and IOV of Bu CL.

Patients and methods:

Retrospective data was derived from 22 pediatric patients (12 males, and 10 females; median age 7.5 years, age range: 0.3 to 13.9 years) who underwent allogeneic hematopoietic stem cell transplantation at the Department of Pediatrics, University Hospitals of Geneva and received intravenous Bu as a component of conditioning. Bu was given in a four times daily dosing schedule and its levels were measured using a validated LC-MS/MS assay.[4] Bu first dose was either age or weight-based and dose adjustment based on the first dose PK parameter estimates was performed. GSTA1 promoter region variants were genotyped by PCR amplification followed by Sanger sequencing to derive functional haplotypes.[5] 327 plasma concentration measurements (173 on the first day, 51 on the second day, 93 on the third day, 8 measurements on the fourth day and 2 measurements on 5th day) were included to be able to explore the IOV and IIV. Age, weight, gender, height, Body surface area (BSA), hematocrit, baseline disease (malignant vs. non-malignant), conditioning regimen (Bu-cyclophosphamide, cyclophosphamide-Bu, Bu-fludarabine) and GSTA1 functional haplotypes (poor metabolizer group, normal metabolizer group, rapid metabolizer group) were evaluated as potential covariates. Bu drug levels and potential covariates influencing drug exposure were analyzed with stepwise covariate modelling on a base model using the nonlinear mixed effects modeling software, NONMEM version 7.3. Plots, visual predictive check (VPC), bootstrap were performed to determine the stability and the reliability of the final model.

Results:

Among the children included, 11 received Bu-cyclophosphamide, 4 received cyclophosphamide-Bu, and 7 received Bu-fludarabine based conditioning. Sixteen of them were diagnosed with malignancies and remaining with non-malignant diseases. Mean hematocrit values were lowered by 15-17% on day 3 from the first day of conditioning with Bu in children receiving cyclophosphamide-Bu and Bu-fludarabine regimen. Bu PopPK was best described by a two compartment model with first order elimination using BSA as covariate on CL. For a typical patient whose BSA is 0.88 m^2, the population values of CL and central compartment volume (Vc) were 2.94 L/h and 10.5 L, respectively. Inter-compartmental clearance (Q) was 0.98 L/h and peripheral compartment volume (Vp) was 50.7 L. IIV and IOV (CV %) of the final model was 22% and 21.8%, respectively. BSA showed slightly more significant influence on CL (reduced variability from 48.1 % to 22 %) and Vc compared to bodyweight. Hematocrit and functional haplotype groups of GSTA1 did not have a significant effect on both IIV and IOV (trend seen of 11%) in this data set.

Conclusions:

BSA significantly influenced Bu pharmacokinetics. Hematocrit and GSTA1 functional haplotype groups did not have a clinically relevant effect on Bu IIV and IOV of PK in this dataset. Small number of patients and use of various conditioning regimens may have influenced the model, and this model performance must be evaluated in a larger dataset.

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I-42: *Piet van der Graaf* Systems pharmacology modelling of the alternative pathway to study target suitability

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Objectives: The complement system (CS) is an integral part of the innate immune system. Its effector functions include pathogen clearance and inflammation. It can be activated via the classical, alternative or the lectin pathways (CP, AP and LP, respectively). The activation signals are then amplified and routed to the downstream terminal pathway by the AP. Dysregulation of the AP is implicated in several autoimmune as well as inflammatory diseases such as C3 glomerulopathy, macular degeneration and asthma [1]. The AP has been recognised as an attractive therapeutic target [2]. Certain potential AP targets exist at high concentration *in vivo*, while certain others display fast turnover. However, such experimental data is not available for the remaining AP targets. Quantitative comparison of suitability of various AP targets using systems pharmacology modelling may be useful in streamlining drug development efforts.

Methods: Towards this goal, we previously built and validated differential-equation-based models of the AP [3]. Two of these models were chosen for this work, namely the minimal model and the steady state model. The minimal model shows the maximal activation response and captures *in vitro* experimental results. The steady state model, on the other hand, simulates the physiological steady state response. We perturbed these two models using hypothetical drugs, considering both small molecule as well as antibody modalities. We used realistic affinities and a range of drug concentrations. We chose the modelled end-point of the pathway as a biomarker with which to study the effects of neutralising various AP targets. We used simulations using typical pharmacokinetic (PK) models for the drugs as well as sensitivity analyses (SA) to rank target suitability.

Results: Using the minimal and steady state models of AP allowed us to study the translatability of target rank-orders between models of an '*in vitro'* versus an '*in vivo*' systems dynamics. AP targets displayed differences in their suitability ranking based on the drug modality. Certain AP targets performed better with small molecule drugs while others performed better with antibodies. Systems pharmacology modelling which included typical drug PK was necessary to capture the effect of target-mediated drug disposition displayed by high abundance targets. Furthermore, we observed that SA and turnover rate on their own are insufficient to predict target rank order, particularly for antibodies. Similarly, baseline target concentration alone was insufficient to predict target rank order for small molecule drugs.

Conclusions: We believe that currently there is no single quantitative measure available, which incorporates the effects of target concentration, turnover as well as its sensitivity. Therefore, it is necessary to perform simulations of the full systems models including a typical PK model for the drugs. We have demonstrated the use of such systems pharmacology models in ranking target suitability using the alternative pathway of the complement system.

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I-43: *Louvina van der Laan* Pharmacokinetics of intracellular stavudine-triphosphate in children after reduced-dose: can we improve stavudine's safety profile?

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Objectives:

Stavudine is being phased out as a first-line ART option due to cumulative mitochondrial toxicity, but it remains an important replacement option for HIV+ children in sub-Saharan Africa. At the recommended dose, it causes stigmatizing lipoatrophy(1–4). A lower adult dose of 30 mg twice daily maintains efficacy, but with less mitochondrial toxicity(5). Although the adult dose was formally reduced in 2007 from 40 to 30 mg twice daily(6), the children's dose (1 mg/kg twice daily) was not correspondingly lowered, due to concerns about efficacy. We therefore compared intracellular stavudine-triphosphate levels in children receiving 0.5-0.75 mg/kg twice daily to adults receiving 30 mg twice daily.

Methods:

23 HIV+ children and 24 HIV+ adults from South-Africa received stavudine at 0.5 mg/kg and 20 mg twice daily for 7 days, respectively. As the study linked with a concurrent adult randomized clinical trial of stavudine 20mg twice daily (NCT02670772), our initial model design was based on adults receiving a stavudine dose of 20mg twice daily. Since no evidence exists to suggest non-linearity, simulations were carried out for adults receiving the current WHO recommended dose of 30mg twice daily. Stavudine suspension was used for children and capsules for adults. Blood samples were taken pre-dose and either at 1, 2, and 6, or 3, 4, and 8 hours post dose. Intracellular stavudine-triphosphate in peripheral blood mononuclear cells was assayed using Liquid Chromatography Tandem Mass Spectrometry. A population pharmacokinetic model was developed to describe the data using Monolix software version 2016R1 and SAEM, together with simulations using the Simulx package in R to explore the effect of dose reduction in HIV+ children.

Results:

Median (interquartile range) age and weight were 8 (7, 9) years and 23 (20, 26) kg in children and 36 (30, 40) years and 83 (70, 98) kg for adults. A bi-phasic disposition model with first-order appearance and disappearance described the pharmacokinetics of stavudine-triphosphate. Accounting for the effect of body size using allometric scaling based on fat-free body mass improved the model fit. No significant differences other than those accounted for with allometric scaling were detected in any pharmacokinetic parameter between adults and children, although a non-significant trend towards children having lower bioavailability was observed. Using a large unrelated adult dataset, simulations of 30 mg twice daily predicted median (IQR) stavudine-triphosphate Cmin and Cmax values of 14 (9, 19) and 45 (38, 53) fmol/10^6 cells. Similarly, simulations in an unrelated dataset of HIV+ children receiving newly proposed weight-band dosing (0.5-0.75 mg/kg) predicted a Cmin and Cmax of 14 (10, 21) and 58 (50, 68) fmol/10^6 cells.

Conclusions:

Pharmacokinetic parameters of stavudine-triphosphate in children receiving the reduced stavudine dose of 0.5 mg/kg twice daily were similar to adults receiving 20 mg twice daily. The trend observed for a lower bioavailability in children may be due to difficulty in drug administration or the different formulations used. Weight band dosing using a stavudine dose of 0.5-0.75mg/kg is proposed as it shows comparable exposures to adults receiving the current WHO recommended dose of 30mg twice daily. Our pharmacokinetic results suggest that the decreased stavudine dose in children >7kg would have a reduced toxic effect while maintaining viral suppression.

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I-44: *Michiel Van Esdonk* Population pharmacokinetic/pharmacodynamic analysis of multiple nociceptive pain models following a single oral pregabalin dose administration to healthy subjects

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Introduction:

Pain models are an objective way to study analgesic effects in addition to the commonly used pain questionnaires in clinical trials. These pain models can be performed, multiple times a day, to investigate analgesic effects and to establish the concentration-effect relationship of novel analgesics. A previous study investigated analgesic effects using a battery of multi-modal pain models [1] for six known compounds, following intravenous or oral administration [2]. A mixed model analysis of variance showed significant analgesic effects on four pain models after oral administration of pregabalin. However, the investigation and quantification of the concentration-effect relationships would provide more information on drug response and the sources of variability in endpoints, compared to the results of statistical testing alone. Therefore, the aim of the current study was to quantify the concentration-effect relationship of pregabalin on the previously identified significant effects on pain thresholds in the cold pressor, electrical stimulation, pressure and contact heat models using population non-linear mixed effects pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Methods:

A single oral dose of 300 mg pregabalin was administered to 16 healthy subjects (8 male and 8 female) in a placebo controlled, randomized, cross-over fashion. On each occasion, a battery of pain models was performed 10 times, up to 10 hours after dosing. Population PK model development evaluated the performance of 1-, 2- and 3-compartment models with (non-)linear elimination kinetics. Lag time and transit compartments were explored to describe the absorption phase of pregabalin. Population PD model development evaluated direct and indirect (turnover) effect models in which a linear- or maximal effect relationship (E_{max}) was tested for the concentration-effect relationship of pregabalin. NLME modeling was performed using NONMEM V7.3 [3].

Results:

The PK of oral pregabalin was best described with a 1-compartment model with lag time, linear absorption and linear elimination. The use of transit compartments for the absorption phase was not superior. Significant inter-individual variability (IIV) was identified on all population PK parameters. The maximum relative standard error (RSE) was 42.4%. The inclusion of weight dependent changes on the volume of distribution and clearance significantly lowered the objective function value (OFV) with 22.4 points.

The cold pressor and electrical stimulation measurements showed a high day-to-day variability within individual subjects. Therefore, between occasion variability was included in both models at the start of model development. For the cold pressor, 148 placebo and 143 pregabalin treated measurements were available for model development. The placebo data were best described using a turnover compartment. A

learning effect between all visits, tolerance over time, or circadian rhythmicity could not be identified. A linear relationship between the pregabalin concentrations and the k_{in} best described the concentration-effect relationship (ΔOFV = -75). All parameters were estimated with low RSE's (<30%).

For the electrical stimulation, 160 placebo, 153 treated measurements were available for model development. The use of a turnover compartment with an E_{max} effect gave a significant reduction in the OFV (ΔOFV = -91.5). However, a low EC_{50} was estimated, indicating that the maximal effect was already reached at the lowest pregabalin concentrations. As such, model development was continued with an on-off effect model, which resulted in a similar OFV and reduced RSE's compared to the full E_{max} model. Population parameters were estimated with low RSE's (<30%).

The PD model development of the pressure and contact heat pain models did not result in the identification of a stable model, due to difficulties in parameter estimation and high levels of variability.

Conclusions:

Two population PK/PD models with significant concentration-effect relationships were developed to describe the effect of oral pregabalin on the cold pressor and electrical stimulation response in healthy subjects. The previously identified significant effects of pregabalin on the pressure and heat pain models could not be confirmed using a population PK/PD modelling approach. The high variability in the baseline response to all pain models suggests that sufficient baseline measurements should be performed at each occasion.

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I-45: *Erno van Schaick* Simulations of the paliperidone pharmacokinetics of intramuscular long-acting injectable microsuspensions of paliperidone palmitate in rats using a mechanistic model

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Objectives: The objective of the present work was to develop a mechanism-based model that can predict the in vivo pharmacokinetic profile of intramuscular long-acting injectable (LAI) microsuspensions of paliperidone palmitate (PP) in rats, based on formulation characteristic, PK parameters of the active compound paliperidone and time-dependent histological parameters related to the local tissue response after intramuscular injection of depot formulations.

Methods: The in vivo release rate of intramuscular long-acting injectable PP microsuspensions in rats was described by a mechanism-based model that consisted of two main parts:

- One part describing drug release based on in vitro performance properties and formulation characteristics such as the intrinsic dissolution rate and particle size distribution.
- A second part, where drug release is orchestrated by the local chronic inflammatory reaction with macrophage infiltration.

Intramuscular injections of clinical 1-month (Xeplion®) and 3-month (Trevicta®) depot formulations of paliperidone palmitate were evaluated in rats. These crystalline suspensions were characterized for their particle size distribution and median particle diameter. Histopathological evaluations of the injection site provided rate constants for infiltration of macrophages into the drug depot, as part of the natural foreign-body reaction to the injection[1,2]. The subsequent release rate of paliperidone from macrophage-encapsulated drug particles was evaluated in an in vitro macrophage-based particle uptake and drug release model. Plasma concentration-time profiles of paliperidone in rats following a single intramuscular injection of 20 mgEq./kg of the 1-month depot and 70 mgEq./kg of the 3-month depot were assessed over a period of 3-12 weeks post-dose. Intramuscular and intravenous administration of a paliperidone immediate release formulation in rats was used to obtain the disposition kinetics of the active compound. The mechanistic model was implemented in Simulo[3] and used to elucidate the key elements that define the observed slow-release kinetics of paliperidone.

Results: Typically, the paliperidone concentration-time profiles in rats were multi-phasic with an initial, short-lasting peak in plasma concentrations occurring within 24-hours, followed by a slow increase in levels with maximum concentrations occurring at 7 to 14 days post injection. The initial fast paliperidone release during the first 24-hours post injection was shown to be mainly driven by dissolution of paliperidone palmitate at the surface of the particles. Simulations indicated that this dissolution driven process occurred slower in vivo and lasted for a relatively short time. The process of the foreign body reaction after injection was shown to be an important driver for the slow release characteristics of the injected PP suspension. The rate of macrophage infiltration of the depot (half-life of infiltration of 3.3-4.4 days for the 1-month depot and 6.1 days for the 3-month depot) and the observed extensive phagocytosis of drug particles[1] provided rate constants for the macrophage uptake. The macrophage infiltration/uptake and release rates were the driving parameters for the observed slow appearance and slow decline of paliperidone in plasma following intramuscular administration of the PP long-acting injectable suspensions.

Conclusions: The present work supports the development of a translational mechanistic model that potentially can predict systemic exposure of novel intramuscular LAI nano-/microsuspensions based on in vitro and in vivo design characteristics and may, as such, support future rational formulation development.

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I-46: *Tamara van Steeg* Development of a mathematical model to elucidate the cross-linking of GSK-057 and ADAs and binding to TNFR1 receptor – filling the gap between hypothesis and reality.

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Objectives: The variable heavy (VH) chain domain antibody (dAb) GSK1995057 (GSK-057) was developed to selectively block TNF-α receptor 1 (TNFR1), thereby antagonising TNF-α signalling. Recently, pre-existing auto-antibodies (ADAs) have been discovered in approximately 50% of the GSK-057-naïve healthy human subjects which together with the dAb were found to cross-link and activate the TNFR1 membrane bound receptor (mTNFR1), leading to symptoms of cytokine release [1]. The aim of the current investigation was to explain the apparent reversible agonistic effects of dAbs in subjects expressing pre-existing ADAs by development of a mathematical framework for the interaction between dAb, ADA and both soluble (sTNFR1) and membrane-bound TNFR1 (mTNFR1).

Methods: A phase I trial investigating the safety and tolerability of GSK-057 in humans provided data on PK, free and total sTNFR1 levels after administration of a wide dose range of GSK-057 (single dose administration, 0.0004 up to 2.0 mg/kg). Moreover, these GSK-057 treated subjects were monitored for the existence of ADAs. Analyses for the Phase I data were performed in NONMEM (Version 7.3, method FOCE with interaction). Model extension based on theoretical considerations, simulations and all graphical explorations were performed using R (version 3.3.2) and Rstudio (version 1.0.44). Relevant model parameters were estimated or obtained from theoretical concepts, literature or in-vitro experiments.

Results: A full TMDD model was used to capture the observed profiles in time for unbound dAb, free and total sTNFR1 following administration of GSK-057. The clearance and inter-compartmental clearance for GSK-057 were estimated 0.0502 and 0.00306 L/h/kg and the estimated volumes of distribution were in the normal range (e.g. Vc = 0.0692 L/kg). The interaction with the target was captured using the *in-vitro* affinity (K_D = 0.0143 nM) and an estimated kon of 0.778 $nM^{-1}.h^{-1}$. Finally, the baseline sTNFR concentration, the degradation rate and the internalization rate were estimated 0.0541 nM, 0.709 and 0.108 h^{-1}, respectively. Although, the biomarker profiles were captured adequately, this analysis revealed that the interaction with the membrane-bound receptor could not be derived from the data. For that reason, the model was extended to capture mTNFR1 binding, GSK-057-ADA complex formation and subsequent mTNFr1 crosslinking, based on theoretical concepts. The final model included (i) the synthesis and degradation of mTNFR1 (ii) the production of sTNFR as a result of shedding of mTNFR1, (iii) the internalization and shedding of the dAb-mTNFR1 complex, (iv) dAb-ADA binding and (v) binding of the dAb-ADA complex to mTNFR1 and, thus, reflected all relevant binding processes involved in the activation of the mTNFR1 by dAbs in individuals with pre-existing ADAs. An iterative simulation process provided insights into the existing knowledge gaps. Simulation results were discussed with the clinical/preclinical project teams regularly, thereby challenging the model against the available knowledge on the system. Finally, a sensitivity analysis further strengthened the parameter space.

Overall, the simulations revealed a bell-shaped binding curve for the dAb-ADA-mTRFR1 complex, thereby demonstrating the reversible nature of the agonistic effects when increasing the dose of the dAb. Furthermore, the simulations provided clear insights into the parameters, which governed the reversible

nature of the agonist effects. For example, the pre-existing ADA were shown to be approximately 10-fold lower in affinity to GSK-057 than it is to TNFr1 and the maximum ADA baseline estimated to be approximately 0.1 nM.

Conclusions: Simulations with the developed mathematical model showed that a reversible agonist effect is indeed to be expected based the underlying biological binding principles and the parameters, thereby filling the gap between hypothesis and reality.

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I-47: *Rob van Wijk* Nanoscale blood sampling from zebrafish larvae for the estimation of distribution volume and absolute clearance

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Objectives:

The use of zebrafish larvae as model system for drug discovery and early drug development is being recognised. It has become clear that internal drug exposure, rather than external exposure, should be studied when investigating pharmacological responses in these studies [1]. Recently the first pharmacokinetic (PK) model was developed using the paradigm compound paracetamol (acetaminophen) in zebrafish larvae of 3 days post fertilization (dpf) [2]. As sampling blood from a larva 1-2 mm in size and only hundreds of nanoliters in volume was not possible at that time, this model was based on total paracetamol amounts in lysed larvae. As a result, distribution volume could not be estimated and only relative clearance values could be obtained. For extrapolation to higher vertebrates, these parameters are however essential. Our aim here is therefore to develop an experimental method to sample blood from zebrafish larvae at 5 dpf in order to estimate pharmacokinetic parameters including distribution volume and absolute clearance.

Methods:

Blood was sampled from different anatomical locations of the larval circulation [3] using a pulled needle (borosilicate glass capillary, original diameter: 0.75 mm. Sutter Instruments) in a micromanipulator, connected to a manual CellTram pump (Eppendorf) under 20x microscopic magnification (Leica). For determination of sample volume, an image was taken of each sample within the needle. To prevent coagulation, different strategies were tested, including heparin coating of needle and collection tube.

In the PK experiment, zebrafish larvae of 5 dpf were exposed to 1 mM paracetamol for 10-170 minutes after which the larvae were washed and the blood was sampled using the optimized blood sampling method. Blood concentrations of paracetamol and its major metabolites were quantified using UPLC (Waters) – MS/MS (AB Sciex). The obtained concentrations were combined with previously gathered data of paracetamol amounts from lysed larvae from an experiment in which larvae were exposed to the same paracetamol concentration for 10-180 min, or for 60 min with a washout period of 60-240 min.

Non-linear mixed effects modelling was performed in NONMEM 7.3, simultaneously fitting paracetamol amounts in lysed zebrafish larvae and paracetamol concentrations in the blood. Paracetamol absorption from the surrounding medium was parameterized as a zero order process. Both one and two compartment models were tested for distribution. For paracetamol elimination linear and non-linear models were tested. Because of destructive sampling, only residual variability could be estimated.

Results:

Blood sampling from the posterior cardinal vein was most efficient and resulted in highest yields. Injection of the sample into a drop of heparin solution (2 uL 5 IE/mL heparin, Pharmacy AZL, Leiden) prevented coagulation and enabled handling of the sample. By pooling 15-35 blood samples, detectable blood concentrations could be reached.

A one compartment model with first order elimination best fitted the data. An additive error was used for paracetamol blood concentrations and combined error for total paracetamol amounts. Volume of distribution was estimated at 1170 nL, when assuming a weight of 299.1 µg [2,4] this yields 3.9 L/kg for zebrafish larvae of 5 dpf. This estimate is in the same order of magnitude as reported distribution volumes of paracetamol in higher vertebrates. Clearance was estimated at 1.8 µL/h, well within the recently published allometric relationship of higher vertebrates' paracetamol clearance [2].

Conclusions:

For the first time, blood samples were taken from zebrafish larvae of only millimetres in size. The development of this technique enables quantification of blood concentration in this new vertebrate model organism, which is critical for estimating distribution and absolute clearance. It shows the potential of systems pharmacology by integration of both experimental and computational innovation.

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I-48: *Marc Vandemeulebroecke* Graphical Principles Cheat Sheet

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Objectives: The goal of this work was to compile a set of Good Graphical Principles concisely and tangibly for everyday use in the production of scientific graphics. Good graphics are at the core of exploring and understanding data, communicating results and conclusions, and ultimately are critical to support decision-making. Hence, due attention should be paid to doing them well – and to understanding what "well" means in the first place. This is the purpose of the Graphical Principles Cheat Sheet.

Methods: A large body of literature and training material, including Tukey (1977), Cleveland (1985), Tufte (2001), Doumont (2009), Few (2012), Krause and OConnell (2012), Robbins (2013), Wong (2013), and Duke et al. (2015), has been condensed into an easy-to-use single-page reference sheet. The various principles have been grouped into sections such as: selecting the right base graph; an effectiveness ranking of graphical attributes (volume, color hue, depth, area, angle, length, position, etc.); how to facilitate comparisons; the best use of color; enhancing legibility and clarity; various implementation considerations; and a checklist for users to assess a graph againstthe most important of these aspects. Each point is illustrated concisely and intuitively with a thumbnail graph. Key references and online resources are included on the sheet as well. Unlike other, more general graphical reference sheets that are available in the world wide web, our Cheat Sheet is tailored for the practicing modeler and statistician in biopharmaceutical sciences and drug development.

The Cheat Sheet has been widely distributed to associates within Novartis as hard copies at a launch event and in electronic format as part of an internal gallery of good graphic examples plus associated code. Workshops have been run for smaller groups of associates, focused on working through an example of how to improve a graph with reference to the points made in the Cheat Sheet. This series of workshops is a key step in ensuring take-up of the messages in the Cheat Sheet and reinforces the idea that the Cheat Sheet is a truly practical tool for improving graphics.

Results: We present and share a carefully designed "Graphical Principles Cheat Sheet" for everyday use in graphical data exploration and the production of graphics for communicating analysis results and conclusions. Our poster re-formats the Cheat Sheet to a large scale, and the Cheat Sheet itself is available as a hardcopy hand-out with the poster. Modelers and statisticians at Novartis now use this Cheat Sheet successfully in their daily job.

Conclusions: A carefully designed single-page reference sheet on Good Graphical Principles is a very useful tool for the creation of clear and impactful graphics. We have had good experiences with our Cheat Sheet at Novartis and now want to share this piece of work for the benefit of a wider audience. We would be interested in an open exchange with other interested parties that may pursue similar goals.

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I-49: *Diego Vera* Disease modelling of repeated acute attacks in an acute intermittent porphyria mouse model

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Objectives: Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder caused by deficient hepatic activity of the porphobilinogen deaminase enzyme (PBGD), the third enzyme in the haem biosynthesis pathway. Precipitating factors such as porphyrinogenic drugs, hormonal changes, fasting, infections, stress, or alcohol intake increase hepatic demand, leading to acute attacks associated to the accumulation of the neurotoxins ALA and PBG [1]. Compound heterozygote T1/T2 mice (AIP mice) exhibit 33% of normal PBGD activity in the liver. In order to biochemically mimic a human porphyric attack, porphyrinogenic drugs are administered to porphyric animals [2]. The aim of this work was to develop a mechanistic disease model to characterise urinary excreted levels of haem precursors (ALA, PBG and porphyrins) during acute attacks in porphyric mice. This model can be used as a platform to explore the impact of different porphyric treatments and guide dose selection.

Methods: Acute attacks were induced at day 1, 9 and 30 in male AIP mice by intraperitoneal injection of four increasing doses of phenobarbital (75, 80, 85 and 90 mg/kg) every 24 hours. Mice (n=12) were housed in metabolic cages in order to collect 24-hour urine, where haem precursors were quantified. A total of 151 ALA, 154 PBG and 149 porphyrin measurements were available for the analysis. Phenobarbital concentrations were not available for the study. Therefore, plasma phenobarbital concentration (C_{Pheno}) profiles were generated using a one compartment model adapted from the literature [3]. It was assumed that phenobarbital was completely and instantly absorbed after an intraperitoneal administration. Data was analysed using the population approach with NONMEM 7.3 software.

Results: Amounts excreted in urine were assumed proportional to (unmeasured) circulating levels of haem precursors with arbitrary values of 1 under unperturbed conditions. In our model, circulating levels of ALA and PBG were considered the precursors of circulating PBG and porphyrins, respectively, with synthesis and degradation rates governed by the K_{MOD} parameter. Phenobarbital increased the synthesis rates of ALA and PBG linearly with respect to C_{Pheno}. Maximum C_{Pheno} levels of 115.23 mg/L exerted a three-fold increase of K_{MOD} with respect to the estimate at baseline (0.0747 h^{-1}). Inter-animal variability (IAV) was found relevant on the synthesis rate constant for urinary ALA and urinary porphyrins (IAV of 15.5% and 21.7%, respectively). Overall, the final model showed a good parameter precision (RSE <30%) and it was able to satisfactory describe the mean tendency and dispersion of the data as confirmed from the visual predictive checks.

Conclusions: A semi-mechanistic pharmacokinetic-pharmacodynamic disease model for acute intermittent porphyria successfully describing the temporal evolution of the haem precursors excreted in urine after repeated phenobarbital-induced acute attacks has been developed. To the best of our knowledge, this model represents the first computational approach to characterise AIP symptoms in porphyric mice. Moreover, it provides a quantitative framework to explore the impact of new therapies for acute intermittent porphyria and to model their effects in restoring haem precursor synthesis.

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I-50: *Swantje Völler* Use of second-to-second physiological monitoring data for continuous evaluation of pharmacotherapy in preterm infants: an application to the respiratory stimulant doxapram

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Objectives: Even at the technically well–equipped intensive care units for newborns infants, drug effect evaluation is mostly based on human interpretation of a selection of patient measurements. Vital parameters from patient's bedside monitors can nowadays be stored on a second-to-second basis, but their use remains mostly limited to the traditional 'snapshot' assessment of a patient's health status. Continuous quantitative analyses of high frequency patient data could not only allow proper timing of pharmacological interventions, but also help to monitor and evaluate the effects of these interventions. Here, we report on a continuous analysis of data for doxapram, a respiratory stimulant. It is used for the treatment of apnoea of prematurity (AOP) in order to keep arterial oxygen saturation (SpO_2) between 89-95% to avoid organ damage by hypo-/hyperoxia [1].

Methods: Second-to-second data on SpO_2, respiratory rate and heart rate from bedside monitors of all preterm neonates, stored in the Erasmus Medical Centre in Rotterdam, were available for evaluation. We extracted data from 24 hours before to 144 hours after start of doxapram therapy in 59 preterm neonates treated from 2014 to 2017. Using R, data were processed and the distribution characteristics for each of the physiological parameters were calculated on an hourly basis. As SpO_2 is the target measure for treatment of AOP, derived parameters were calculated for SpO2: the cumulative time of SpO_2 below the saturation target (89%) per hour [sec/h], the number of times a child dropped below the target value and the area under the curve (AUC) of each saturation dip below the target value. To quantify the immediate effect of doxapram, values in the last hour before and after start of doxapram were compared using a Wilcoxon rank sum test in R. The same was done for 24 h after start of doxapram and 144 h (6 days) after start of doxapram. Potential effect parameters were correlated to the administered dose and the potential differences between oral and intravenous administration, and patients with and without a loading dose were evaluated.

Results: In the hour after start of doxapram treatment, SpO_2 increased significantly ($p<0.01$), while respiratory rate and heart rate remained unaffected. The same was true when comparing the hour before start of treatment to later time points (24 h and 6 days after start of therapy). When looking at the AUC of each saturation dip below the SpO_2 target value, the number of dips and the duration of an SpO_2-dip below 89%, all three parameters decreased significantly during the first hour of treatment ($p<0.01$ in all cases). The median decreases were 61.4%, 45.9% and 21.5%, respectively. 144h after start of treatment, the AUC and duration of dips were still significantly lower than before start of therapy, while the number of dips did not differ significantly anymore. Oral administration led to a lower median reduction in AUC during the first hour of treatment than intravenous administration (75.0% vs. 42.7 %) which seems to disappear 24h after start of medication. The administration of a loading dose did not show any pronounced differences in reduction of AUC.

Conclusions: Using high-frequency monitoring data, we showed detailed effects of doxapram over time, which will be linked to pharmacokinetic data in the future. We could objectively determine the respiratory condition and the effects of doxapram treatment in preterm infants on an hourly basis. This type of analysis might help to develop individualized drug treatments with tailored dose adjustments based on real-time physiological monitoring of a patient, using a closed-loop algorithm.

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I-51: *Veronika Voronova* Using a physiologically-based QSP model to simulate the effects of perturbations of the enterohepatic circulation of bile acids

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Objectives: Bile acids (BA) represent a diverse class of cholesterol metabolism end products undergoing enterohepatic circulation (EHC), with a primary function in maintaining intestinal lipid emulsification. Additionally, BA have pro-tumorigenic, pro-apoptotic and laxative activities; they also activate farnesoid X receptors (FXR) involved in metabolic regulation [1]. Thus, abnormalities in BA biotransformation and distribution within EHC may be associated with pathological conditions including colorectal cancer, hepatic failure, diarrhea. The aim of the current study was to develop a physiologically-based quantitative systems pharmacology (QSP) model allowing for simulations of the three main BA (cholic (CA), chenodeoxicholic (CDCA) and deoxycholic (DCA) acids) dynamics, within EHC, under various conditions.

Methods: The proposed model consists of a system of differential equations describing un(conjugated) CA, CDCA and DCA distributions within the circulation system (systemic; portal serum; sinusoidal space), the hepato-biliary system (liver; bile duct; gallbladder), and the gastro-intestinal (GI) tract (upper and lower intestine; colon). The physiological backbone of the model was based on a model proposed by Hofmann et al. [2]. Briefly, primary BA (CA and CDCA) are formed in the liver, conjugated, stored in the gallbladder, released into the intestine and efficiently reabsorbed, with a minor fraction reaching the colon. Within the GI tract, BA undergo microbial biotransformation: colon is the main site of BA deconjugation and secondary BA (DCA) formation; a minor BA fraction is deconjugated in the lower intestine. Synthesized DCA is reabsorbed in colon or excreted with feces. Food intake promotes gallbladder contraction and stimulates BA release into the small intestine. Postprandial increase of transintestinal BA flux is followed by FXR activation, mirrored by plasma fibroblast growth factor 19 (FGF-19) increase and accompanied by inhibition of cholesterol 7-hydroxylase (CYP7A1) – a major regulatory enzyme in BA synthesis.

Physiological parameters, including organ volumes, plasma flow rates and GI transit time were taken from the literature. Other parameters, corresponding to BA transport and biotransformation, were estimated based on: (1) experimental measurements of BA in different compartments of healthy volunteers (HV); (2) experimental estimates of intestinal and colonic BA permeability. Serum 7α-hydroxy-4-cholesten-3-one (C4) and FGF-19 measurements obtained from HV and patients with EHC abnormalities were used to quantify the effect of FXR activation on BA synthesis.

Results: The model adequately reproduced BA levels in systemic and portal serum, liver, duodenal bile and the GI tract, and predicted average daily BA, FGF-19 and C4 dynamics in serum of HV. Higher fractional hepatic uptake of CA *vs* CDCA and DCA (89% *vs* 77 and 75%, respectively) and conjugated *vs* unconjugated BA (81 *vs* 57%) drove the differences in BA composition between systemic and portal circulation, which is in agreement with experimental data presented previously [3]. Daily BA profiles in systemic circulation and portal vein were similar. Based on model simulations, we also observed spatial differences in individual BA absorption from the GI tract: ileum is the only site of CA absorption, whereas CDCA and recirculated DCA are absorbed throughout the small intestine. Colon is the main site of *de novo* synthetized DCA absorption.

Decreased intestinal BA absorption observed in patients with idiopathic BA malabsorption or illeal resection was simulated using the model. Approximately 50% reduction of BA absorption in the lower intestine was followed by colonic BA accumulation, sufficient to stimulate water secretion and induce diarrhea (~ 2mM). Transintestinal BA flux reduction was accompanied by FXR inhibition and an up to 17-fold compensatory BA synthesis stimulation enhancing colonic BA delivery. According to model simulations, FXR stimulation was shown to reduce colonic BA delivery, which supports this therapeutic approach for treatment of BA induced diarrhea.

Conclusions: A QSP model was used to simulate BA dynamics within EHC and identify factors associated with abnormal BA distribution. According to simulations, insufficient FXR activation in patients with BA malabsorption is a key component of colonic BA accumulation.

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I-52: *Johan Wallin* Validation of Xenograft Dose Predictions for Clinical Efficacy in NSCLC

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Objectives:

The xenograft mouse model is widely used to study the response to cancer therapy. Pharmacokinetic-pharmacodynamic (PKPD) modelling of xenograft data can be performed to predict the exposure level to target in the clinical setting. However, how well these dose predictions translate to clinical efficacy is not well studied although previous attempts have been done. One example is the work done by Rochetti et al[1] where they demonstrated a good correlation between preclinical potency parameters and exposure obtained at therapeutic doses in the clinic for a range of cytotoxic agents.

The objective with this work was to further evaluate the correlation between preclinical and clinical efficacy estimates, including targeted agents representing both small molecules and biologics. Preclinical efficacy estimates derived from xenograft experiments across a range of cell lines, as well as clinical efficacy estimates from failed or successful late phase drug development programs in NSCLC, were collected from both in-house data as well as published data.

Methods:

One central task in this work was to collect data on preclinical and clinical efficacy estimates. The literature was surveyed for oncology compounds with Phase 3 results in NSCLC published in the last 10 years (2006-2016). In addition, a selected number of standard of care compounds were included in the analysis. Substances of interest were targeted kinase inhibitors, monoclonal antibodies (mAbs) and cytotoxics.

The preclinical anti-tumor potency parameter k_2, derived using the model developed by Simeoni et al [2], was of primary interest as an efficacy estimates. Ideally, preclinical k_2 values should be directly compared to translated clinical k_2 estimates. However, due to limitations in the clinical information, clinical EC_{50}-values were used. For approved compounds with no identified exposure-response (ER) it was assumed that EC_{50} was less than lowest exposure quartile in the effective dose. For failed compounds with no identified ER it was assumed that the EC_{50} was higher than highest exposure quartile for the tested dose.

The analysis of correlation of preclinical-clinical efficacy estimates was performed in NONMEM (version 7.3.0). The regression was performed on log-log scale and the M3 method was used to account for the cases where the EC_{50} was assumed to be less than lowest exposure quartile or higher than the highest exposure quartile observed.

Results:

In total, 33 approved, 17 failed and 15 standard of care compounds in various indications were identified. The type of clinical ER information reported varied between the compounds, including E_{max} type of modelling, time-to-event analysis, logistic regression using a cut-off concentration to cases with no published ER information. In total, 9 NSCLC compounds had sufficient information to be included in the

correlation analysis. The correlation between preclinical k_2 estimates and clinical EC_{50} estimates was found to be relatively high (r = 0.90).

Conclusions:

A relatively strong correlation was found between the preclinical and clinical efficacy parameters, supporting the use of xenograft models to predict clinical therapeutic doses. However, this analysis was limited to data from only 9 compounds and based on only one k_2 estimate from one single cell-line for each compound. Further work is ongoing to include data from additional cell-lines for each compound.

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I-53: *Evan Wang* Model-based assessment of QT interval correction methods

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Objectives: ICH S7B and E14 guidances require that all compounds without intended effects on cardiac electrophysiology undergo ventricular repolarization safety assessment through measurement of the QT interval of the electrocardiogram. Given the interdependency of the duration of the QT interval with heart rate, a multitude of correction techniques are used in both clinical and nonclinical trials. Utilizing real beat-to-beat heart rate data and a human ventricular action potential model, the objectives of this work were twofold: 1) demonstrate performance of standard fixed factor and linear regression QT correction methods, and 2) evaluate which method is optimal for correcting the QT interval with drug effects on heart rate and/or ventricular repolarization.

Methods: A simulation-based approach allows known repolarization and heart rate changes to be applied. Different correction methods can then be compared to the known change. Continuous 24-hour beat-to-beat heart rate data from a 64-year-old female was used to calculate QT intervals for a variety of theoretical cardiovascular drug effects (human ether-a-go-go or hERG channel inhibition at 10, 20, 30%, heart rate increase at 10, 20, 30%, and a combination of the two effects). Heart rate and percent hERG inhibition were used as inputs into the O'Hara-Rudy human ventricular action potential model [1], further modified by Dutta et al [2], outputting the corresponding APD90 value (time to repolarize 90% between the peak and resting potential), which is then converted to a QT interval using a human reference value. For all cases (control, drug effects), the QT intervals were then corrected to 60 beats/min using four methods (Bazett's, Fridericia's, linear regression using control slope, linear regression using treatment slope). This exercise was repeated for 1-minute averages of the beat-to-beat data to mimic standard laboratory practices.

Results: Correction methods were assessed based on accuracy (deviation from the "true" modeled interval) and precision (standard deviation of corrected QT intervals). The reported results [lower, upper] reflect the range for the 9 theoretical cardiovascular drug effect scenarios listed above. For both beat-to-beat and 1-minute averaged heart rate data, linear regression using the treatment slope is shown to be overall the most accurate (beat-to-beat: [-11.4, -3.0] ms, 1-min-avg: [-21.6, -6.7] ms) and precise method (beat-to-beat: [3.2, 5.3] ms, 1-min-avg: [3.8, 8.0] ms). Bazett's method was the least accurate producing the highest standard deviation (beat-to-beat: [12.6, 26.5] ms, 1-min-avg: [15.8, 31.3] ms) and consistently over-predicted the QT interval (beat-to-beat: [32.3, 57.9] ms, 1-min-avg: [28.0, 56.6] ms). Fridericia's method performed better than Bazett's method but still produced higher standard deviation (beat-to-beat: [4.0, 9.6] ms, 1-min-avg: [7.32, 14.48] ms) and over-predicted the QT interval (beat-to-beat: [9.4, 15.7] ms, 1-min-avg: [8.6, 15.4] ms). Linear regression using the control slope was similar in accuracy (beat-to-beat: [-17.5, -3.4] ms, 1-min-avg: [-25.4, -8.3] ms) and precision (beat-to-beat: [3.3, 7.7] ms, 1-min-avg: [4.38, 9.45] ms) compared with treatment slope. Unlike Bazett's and Fridericia's methods, linear regression using control or treatment slopes under-predicted the modeled interval, although both methods were closer in magnitude. In cases where there is hERG inhibition with and without heart rate increase (slope of the treatment changes relative to the control), correcting based on the treatment slope showed the smallest standard deviation and was consistently closer to the true simulated data. The relative accuracy increases with increasing hERG inhibition. Only when the QT interval was modified solely by heart rate increase did linear regression using control slope show greater accuracy than using the treatment slope.

Conclusions: Combining real beat-to-beat heart rate data with a human ventricular action potential model convincingly shows that using the treatment slope is the optimal method to correct QT interval measurements. Additionally, this work provides a means to compare heart rate correction methods and to understand the limitations of applying certain methods when they are the only methods feasible.

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I-54: *Shijun Wang* A comparison between nonlinear mixed effects and naïve pooled data methods in population PK model selection

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Objectives: It is recognized that nonlinear mixed effect (NLME) models are a more appropriate representation of data from multiple subjects than naïve pooled data (NPD) models. However, given that NPD models have shorter runtimes and are more robust, there may exist an advantage to use them for model building decisions when NLME models are too run-time intensive or when high robustness is sought, as in automatic model building algorithms. However, the use of NPD models as proxies for NLME models depend on the similarity one can expect in the relative goodness-of-fit of contenting models. Therefore, this study aims to explore how similar model selection is between NLME and NPD models.

Methods: NLME and NPD were compared for 13 previously developed population pharmacokinetic (PPK) models based on real data. Each developed model was structurally divided into 4 parts, which contained the following components: oral absorption delay, absorption rate, distribution and elimination. For the 13 original models, 42 test models were generated by iteratively changing one of the components. The test models and original models were fit to the corresponding real data using both NLME and NPD methods, followed by the calculation of the difference of objective function value (OFV) and Akaike information criteria (AIC) values between each test model and its related original model for NLME and NPD separately (the OFV or AIC of test models minus original models). Model selection criteria was then performed using the likelihood ratio test (5% significance level) as well as choosing the lowest AIC value of the compared models. In a second step, simulation studies were performed to test the sensitivity of the NLME and NPD methods to identifying different model structures. A “full” PPK model with 2-compartment distribution kinetics, non-linear elimination and a transit-compartment first-order absorption model was used to simulate relatively densely sampled data. By varying parameters in the “full” model, characteristics of the model could be emphasized or hidden. For example, by varying the Vmax and Km in the Mechaelis-Menten elimination kinetics, one could mimic first order or zero order elimination, given the dose amount. Similarly, by varying the inter-compartmental clearance Q, one could hide or emphasize the 2nd elimination phase of the “full” model. Relevant reduced models (one-compartment, linear elimination, no transit compartment, zero order absorption) as well as the “full” model were then fit to the simulated data and the ability of the NPD and NLME methods to detect the true “full” model were compared using OFV and AIC values as in the real data examples.

Results: In the comparison of real data, the range of difference in OFV were -101 ~ 2775 and -52 ~ 2332 for NLME and NPD respectively and the model selection of the two methods was consistent for 38 out of 42 test models. For AIC, the model selection was consistent between NLME and NPD for 36 out 42 test models. In 3 out of the 4 differences between NLME and NPD in the OFV comparison and in 4 out of the 6 differences in the AIC comparison, the differences occurred when the test model and original model differed in the structure of the distribution model, which indicated that differences might exist in the selection of the distribution model when using NLME or NPD. For simulation data sets, the average difference in OFV when comparing a 2-compartment (“full”) model and a 1-compartment alternative were -224 (-310 ~ 0.06) and -62 (-152 ~ 45) for NLME and NPD respectively, showing the relatively lower power for NPD to identify a more complex distributional model.

Conclusions:NPD can act as an aid for NLME in PPK model building in terms of model structure selection. Nevertheless, the selection of the distribution model by NPD needs extra attention.

I-55: *Roeland Wasmann* Normal fat mass cannot be reliably estimated in typical pharmacokinetic studies

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Objectives:

Choosing the correct size descriptors for your pharmacokinetic model is important, especially for drugs with a narrow therapeutic index (e.g. aminoglycosides),. Like humans, body size descriptors come in many shapes and sizes, with total body weight (TBW) and fat-free mass (FFM) currently being most accepted [1, 2].

Recently, estimation of normal fat mass (NFM) has been advocated [3]. The NFM size descriptor is the sum of the predicted FFM (based on height, weight and sex) and the estimated relative contribution of fat mass. This method is increasingly employed [4-15].

NFM is estimated using equation 1, where F*fat* reflects the contribution of fat relative to FFM.
NFM=FFM+F*fat**(TBW-FFM) [eq.1]

F*fat* can be considered a drug-specific parameter, suggesting that it can be used for extrapolation of the pharmacokinetics to populations with different body sizes [3]. It remains unclear whether NFM (with estimation of F*fat*) can be reliably estimated in typical pharmacokinetic studies although it can be highly relevant in dose selection. Therefore, we investigated the identifiability of NFM in typical pharmacokinetic studies.

Methods:

As a best case scenario**,** we simulated pharmacokinetic data from a 1-compartment model with first order elimination, a clearance (CL) of 0.693 L/h, volume of distribution (V) of 1 L, inter-individual variability (IIV) of 30% on CL and V, and proportional residual error of 15%. Rich time-concentration data after a single bolus of 1 mg were simulated over a time span of 3 half-lives (n=8 samples). We investigated the identifiability of F*fat* in 16 virtual drugs consisting of all possible combinations of F*fat* of 0, 0.5, 1 or 5 for CL and V.

We chose a balanced study population containing individuals with a wide range of body sizes: each pharmacokinetic study consisted of three arms (50% male): 1/3 non-obese (BMI 18.5-30 kg/m^2), 1/3 obese (BMI 30-40 kg/m^2) and 1/3 morbidly obese (BMI >40 kg/m^2). Real body size data for each population were randomly sampled from the NHANES database [16].

First, for every 16 virtual drugs we simulated 1000 large studies containing 10,000 individuals each, this served as a reference confirming that F*fat* could be identified at all. Next, we simulated 1000 typical studies containing 30 subjects per study. After simulation, we re-estimated all parameters (allometric coefficients fixed) using PsN 4.7.0 and NONMEM 7.3.0 with FOCE-I. We calculated median estimates and the 95% estimation interval (EI) for each drug and each of the two study sizes (large and typical). Feasibility was

tested by comparing the 95%EI with specific feasibility criteria for each value of F*fat*. Feasibility test was passed when the 95%EI was within the bounds of a criterion of -0.25-0.25, 0.25-0.75, 0.75-1.25, and >2 for an F*fat* of 0, 0.5, 1, and 5, respectively.

For sake of simplicity, here, we report only identifiability of F*fat* in typical studies of four virtual drugs where F*fat* combinations were equal for both CL and V.

Results:

For the large studies with 10,000 subjects we found an unbiased estimated of F*fat* with a high precision and all within the feasibility criteria. The identifiability of the estimated F*fat* on CL in a typical PK studies was poor with median [95% EI] of 0.0 [-0.4-0.9], 0.5 [-0.1-2.1], 1.0 [0.1-4.4] and 5.4 [1.3-3.3*10^8] for the drugs with F*fat* of 0, 0.5, 1 and 5 for CL. Although the observed bias was minimal, a high imprecision was observed. Poor identifiability was observed for F*fat* on V with a median [95% EI] of 0.0 [-0.3-0.5], 0.5 [-0.1-1.6], 1.1 [0.3-3.0] and 5.2 [1.5-85] for a simulated F*fat* of 0, 0.5, 1 and 5, respectively. Similar results were observed for the other virtual drugs.

Conclusions: We have shown that the identifiability of F*fat* is excellent in (unreasonably) large studies. High imprecision, however, was observed for estimates of F*fat* in more realistic studies. This could have consequences for dosing drugs with a narrow therapeutic index, especially at extreme weights. Therefore, NFM must be used with caution and, when used, one should consider the power of a study to reliably estimate NFM.

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I-56: *Sebastian Weber* Supporting drug development as a Bayesian in due time?!

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Objectives:

Bayesian approaches give the pharmacometrican additional control over models and can greatly facilitate model based drug development, e.g. partial pooling of few data-sets is a key strength. However, Bayesian approaches are often hampered by their enormous computational burden which can quickly become a problem as model evaluation times easily exceed days for ODE based models. I will present solutions to these practical problems at the example of Bayesian aggregation of average [1,2] data into a population non-linear mixed effect model. In will briefly introduce the Bayesian aggregation of average data approach and then describe generally applicable approaches which reduce the computation time from days to less than one hour. These include analytical shortcuts, approximations and a demonstration of the recently available parallelization technique in Stan [3].

Methods:

As generic example for a pharmacodynamic model an ODE based turn-over model is used. The data-set comprises about 1300 patients from three different studies which collected per patient monthly observations over a year of follow-up time. As the individual pharmacokinetic data was infeasible to measure, a simple one-compartment model was used with known typical patient parameter estimates as input for the turn-over pharmacodynamic model. The average data of an equivalent of 1200 patients was included in the model likelihood, using a nested simulation approach during MCMC integration with Stan.

Results:

The model was expressed using a single ODE for the turn-over equation while the one-compartmental pharmacometric model was solved analytically. Still, the model evaluation time on the individual patient data alone took 2.5 days when using the non-stiff Runge-Kutta 4/5 ODE solver in Stan. However, approximating the concentration time curve by a suitably chosen step function allows to analytically evaluate the turn-over equation in a stepwise manner. This lead to an 8x speedup in model evaluation to only 8h runtime while providing matching results. The accuracy of the approximation can be controlled by decreasing the time step size used in approximating the concentration time curve. A further approach is offered by the current development version of Stan which can perform within chain parallelization using the message passing interface (MPI). Applying MPI parallelization to the ODE based model resulted in a 62x speedup on 80 cores and a net runtime of just one 1h. For the analytical approximation model an 11x speedup on 15 cores was feasible which corresponds to only 45 minutes execution time.

Conclusions:

Excessive running times are an issue for wide spread adoption of any modeling technique. This has been a major drawback of Bayesian approaches for pharmacometricians. I demonstrate how analytical shortcuts or approximations can reduce or avoid the need for computationally intensive ODE solutions. While these techniques are generally applicable, they may require substantial investment of the modeler to work out

problem specific analytical solutions. Thus, the availability of within-chain parallelization in Stan is a critical feature which enables reasonable running times for ODE based models in Stan.

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I-57: *Sebastian Wicha* Handling inter-occasion variability in model implementation for Bayesian forecasting: A comparison of methods and metrics.

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Objectives: Inter-occasion variability (IOV) can substantially impact the accuracy and precision in Bayesian forecasting (BF) in the context of therapeutic drug monitoring. A number of approaches exist to handle IOV when utilising a model for BF, which include ignoring IOV, weighting functions, or variations of accounting for IOV during Bayesian estimation. In this study, we aimed to compare five methods for handling IOV using different metrics in simulations and in a real dataset example.

Methods: A 1-compartment population PK model (CL: 5 L/h, V: 20 L, interindividual variabilities (variance) IIV_{CL}: 0.1, IIV_{V}: 0.1, varying IOV_{CL}: 0.0-0.1, proportional unexplained residual variability (RUV_{prop}) 10 %CV) was used for simulations using a rich (8 samples over 8-hourly dosing) and a sparse sampling design (2 samples at 1 h and 7 h post dose) in 1000 subjects. The real dataset arose from 423 patients and a total of 2422 samples developed a 2 compartmental PK model [1]. All simulations, estimations and forecasting was performed in NONMEM® 7.4.1.

Forecasting of occasion 6 PK for every individual using data from occasions 1-5 (simulation study) or of occasion 3 PK from occasions 1-2 data (real data) was assessed.

The methods to handle IOV tested here were:

(i) 'True' model with IIV and IOV, quantifying η_{IIV} and η_{IOV}'s, but using only η_{IIV} for forecasting

(ii) IIV + IOV: adding ω^2_{IOV} to ω^2_{IIV} together

(iii) IIV-only1: re-estimation of a model without IOV, using the new parameters for forecasting

(iv) IIV-only2: setting ω^2_{IOV} to zero

(v) IIV-only3: weighting down samples from past occasions by doubling RUV for each past occasion

The metrics to evaluate the forecasting accuracy were:

(a) rBias/rRMSE calculated based on the individual predicted vs. observed concentration at the forecasted dosing occasion, and

(b) rBias/rRMSE calculated based on the estimated individual PK parameter (without η_{IOV}) versus the true parameter (simulation study) or the individual PK parameter determined from the final published model (real data).

Results: Increasing IOV increased rBias/rRMSE in all metrics. In simulation (IOV of 0.1, rich design) metrics (a) displayed a positive bias in all scenarios with method (v) being least biased (rBias: 44%, rRMSE: 477%), followed by (i) (46.7%, 469%), (iii) (63.1%, 625%), (ii)=(iv) (80.6%, 693%). For metrics (b), individual CL

determined by method (i) was least biased (CL: 0.4%, 13%; V: -0,74%, 4.3%), followed by (iii) (CL: 3.2%, 15.1%; V: 18.5%, 23.5%), (iv) (CL: -6.2%, 15.2%; V: 9.9%, 16.8%), (ii) (CL: -6.2%, 15.2%; V: 9.9%, 16.9%), (v) (CL: 10.1%, 23.6%; V: 23.7%, 30.8%). Similar results were obtained with the sparse simulation data.

Using real data, metrics (a) also displayed a positive bias in all scenarios. Method (v) was least biased (17.2%, 146.4%), followed by (i) (20.6%, 154.5%), (iii) (27.5%, 179.7%), (iv) (30.8%, 168.4%) and (ii) (32.4%, 173.5%). For metrics (b), method (i) was least biased (CL: 1.2%, 6.0%), followed by (ii) (CL: -2.2%, 13.3%), (iv) (CL: -2.6%, 10.8%), (v) (CL: 2.8%, 7.9%) and (iii) (CL: 3.2%, 11.7%).

Conclusion: Similar trends in forecasting accuracy were observed in the simulation study and the real dataset, but less marked in the latter. Metrics (a), although popular and frequently used, was intrinsically biased in presence of IOV and hence should be interpreted with caution. Metrics (a) suggested the weighting approach (v) to outperform the true model (i) in the simulation study. Comparisons on the forecasting performance of models on the level of estimated vs. true individual PK parameters, i.e. metrics (b) might be more meaningful, but susceptible to shrinkage. Overall, method (i) displayed the best forecasting performance. Method (iii), where IOV was not estimated may be preferable over the weighting method (v) in presence of IOV.

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I-58: *Mélanie Wilbaux* Risk score based on survival multivariate analysis of baseline patients' characteristics reduces variability in a PKPD model of tumor growth inhibition

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Objectives:

(i) Develop a PKPD model of longitudinal tumor size in hepatocellular carcinoma (HCC) patients receiving FGF401, an oral FGFR4 kinase inhibitor under evaluation in a phase I/II study (NCT02325739); (ii) identify clinical baseline characteristics and derive a continuous risk score predictive of time to progression (TTP) using multivariate analysis; (iii) evaluate this score as a covariate on PKPD model parameters, and (iv) simulate tumor kinetics at different patients characteristics and support dosing regimen optimization for future studies.

Methods:

Plasma concentrations (n=2188) time course, longitudinal tumor size (n=273) and individual baseline characteristics data were collected from 71 HCC patients, with FGF401 once-daily doses from 50 to 150 mg. Pharmacokinetics and tumor growth models were developed using non-linear mixed-effects modeling implemented in Monolix 2016R1. A sequential PKPD model approach was used with PK parameters fixed at an individual level in the PKPD modeling analysis. A total of 82 patients' baseline characteristics were included to develop a parsimonious predictive model for TTP using robust statistical approach with cross-validation methodology [1]; All statistical computations were carried out in R-3.2.3. A continuous risk score was derived and evaluated as a covariate on key parameters of the PKPD tumor growth inhibition model. Final PKPD model evaluation and selection were based on statistical criteria, goodness-of-fit plots and simulations based diagnostics. The final PKPD model was implemented in a Shiny application [2, 3] to simulate tumor growth inhibition at different doses, regimens and given patients' baseline characteristics.

Results:

A two compartment model with a delayed 0-order absorption and linear elimination was adequately describing PK data. Unperturbed tumor growth was best characterized by a fist-order process. Plasmatic PK was linked to the tumor-killing rate through an effect compartment to reproduce a delay before drug effect. A resistance component with parameter λ was added to describe the tumor regrowth under treatment [4]. Multivariate analysis resulted in three baseline predictive factors of TTP: (1) adjacent organ invasion (e.g. gallbladder and peritoneum), (2) number of target lesions, and (3) number of metastatic sites. The dose was also found as a predictive factor of TTP, reinforcing the value of a PKPD model development. A continuous risk score was derived excluding dose to avoid any bias with PKPD model integration. The risk score was found to be a significant covariate on the resistance parameter λ (p=5e-05) and baseline tumor size (p=6e-07). Inter-individual variability on λ parameter was reduced from ω = 0.7 to ω = 0.5. All goodness of fit plots were improved after inclusion of the risk score. Simulations from the PKPD tumor response model supported the selection of 120mg daily as the recommended dosing regimen for future studies.

Conclusions:

Multivariate analysis using a robust statistical approach suggested a possible set of covariates for a PKPD tumor response model. The multivariate composite risk score was highly significant as a covariate on the resistance parameter, resulting in reduction of variability and PKPD model improvement. The final PKPD model implemented in a simulation tool was used to support dosing regimen selection for given patient populations. The proposed methodology, combining multivariate analysis and PKPD modeling on related endpoints (e.g. TTP and tumor size), can be applied for other efficacy and safety endpoints.

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I-59: *Justin Wilkins* Population pharmacokinetic analysis of M7824 (MSB0011359C) in different cancer types

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Objectives: M7824 is an innovative first-in-class bifunctional fusion protein composed of a human IgG1 monoclonal antibody against programmed death-ligand 1 (PD-L1) fused with 2 extracellular domains of transforming growth factor-beta (TGF-β) receptor II to function as a TGF-β "trap" and has shown promising antitumor activity and manageable safety in phase 1 trials [1]. A population pharmacokinetic (popPK) analysis of M7824 was conducted to assess covariate relationships and time-varying clearance (CL) and to support dosing strategy.

Methods: Pharmacokinetic and covariate data from 644 patients with various solid tumor types enrolled in 2 phase 1 clinical studies of M7824 (NCT02517398 and NCT02699515) were used to develop the popPK model using NONMEM software. Patients received intravenous bi-weekly doses of 0.3, 1, 3, 10, or 20 mg/kg, 500 mg, and 1200 mg for 1 to 58 weeks (as of the analysis cutoff date). Two-compartment models with support for time-constant and alternative time-varying clearance (CL) [2], target-mediated drug disposition (TMDD) and time-varying covariate models [3] were investigated during the analysis. A full covariate modeling approach was followed, in which all covariates of interest were tested on CL and central volume of distribution (V1) simultaneously.

Results: A 2-compartmental linear model was found to provide the best description of M7824 concentration. In the typical patient, CL was estimated to be 0.0158 L/h (relative standard error [RSE], 4.1%; interindividual variability [IIV], 8.1%), V1 to be 3.21 L (RSE, 3.2%; IIV, 8.6%), peripheral volume of distribution (V2) to be 0.483 L (RSE, 9.8%; IIV, 17.5%) and intercompartmental clearance (Q) to be 0.00512 L/h (RSE, 12.3%; IIV, not estimable using these data). Covariates estimated to produce a median change in CL of >10% at baseline, with an asymptotic confidence interval excluding the no-effect value, included body weight (BW), sex, albumin, C-reactive protein, platelet count, tumor size, and tumor type (glioblastoma). Covariates affecting V1 to a similar degree included BW, sex, albumin, and tumor type (pancreatic cancer). BW was the most influential covariate, producing median increases > 20% in both CL and V1 at the high extremes of weight in the population. Both CL and V1 were increased in patients enrolled in the ascending-dose phases of the trials. Incorporation of time-varying clearance models did not result in any significant model improvement, despite widespread prior observation of this behavior in other drugs acting on PD-1 and PD-L1 [2], although treatment duration was relatively short in most subjects included in the current analysis population. Models incorporating TMDD and time-varying covariate effects [3] failed to provide improvement to the model. The results of simulations from the model suggested that the variability in exposure was slightly higher with BW-based dosing than with flat dosing.

Conclusions: The linear popPK model for M7824 described the observed data well and was applied to inform dosing strategy. Simulations demonstrated that variability in exposure was slightly higher in regimens applying body weight-based dosing than in regimens applying flat dosing.

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I-60: *Francis Williams Ojara* A time-to-event analysis of paclitaxel-related peripheral neuropathy in patients with advanced non-small cell lung cancer receiving first line chemotherapy

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Objectives:

Peripheral neuropathy (PN), a dose-limiting adverse event of paclitaxel (PTX) affects > 20% of patients on PTX therapy and negatively impacts quality of life. Covariates e.g. PTX dose and time of plasma concentration above 0.05 µM have previously been identified as influential by comparing odds of PN for patients at different covariate levels [1,2,3]. However, the above analyses do not account for impact of time on treatment and censored observations (unknown incidence times) on the risk of PN. The aim of this analysis was to describe the time-course of occurrence of clinically important PN (CIPN, grades 2 or 3) and explore the influence of different treatment and patient characteristics on the risk of CIPN to support dose adaptation and hence reduce the occurrence of PTX-associated CIPN.

Methods:

Patients from the CEPAC-TDM study (n = 366), who received PTX in combination with carboplatin or cisplatin every 3 weeks for ≤ 6 cycles [4], were included. PN symptoms, severity, start and end dates were recorded and classified using the common toxicity criteria (version 4.0) [5]. Time-to-event (TTE) analysis was employed to describe the risk of incidence of CIPN (event) during treatment. Constant, Weibull, Gompertz and cycle-varying hazard models were examined. Impact of covariates, PTX dose, age, weight, sex, and smoking status were jointly evaluated in a full covariate model [6] with covariate selection based on prior clinical and mechanistic knowledge, and information content of the different covariate categories. Statistical and clinical significance of covariates were derived from the distribution of hazard ratios corresponding to different covariate levels. Statistical significance was attained if distribution of hazard ratios didnot include 1 (the null value) whereas the region of clinical significance was set to +/- 20% of the null value. The PTX dose-CIPN risk profile was further explored by simulating incidence of CIPN at two clinically relevant dose levels: 200 mg/m^2 and 175 mg/m^2, with a standard treatment schedule (6 cycles, 21 days each). Dataset formatting was performed in R (3.4.3) and TTE analysis in NONMEM (7.3.0).

Results:

105 PN events were reported with generally higher incidences at cycle start and gradual decline across the cycle. The cycle-varying hazard model, describing a surge in risk of CIPN at cycle start and gradual decline across each cycle, best captured the data. PTX relative dose and age had both statistically and clinically significant impact on the risk of CIPN whereas weight, sex and smoking status were not statistically significantly associated with CIPN. A 19% increase in risk of CIPN with 200 mg/m^2 over 175 mg/m^2 was predicted: hazard ratio (95% CI), 1.19 (1.06, 1.33). The risk of CIPN increased with age. There were also trends towards increase in risk of CIPN with increased weight and smoking status. Since platinum drug type (cisplatin or carboplatin) and diabetic status (diabetic or non-diabetic) had unbalanced proportions (less

than 20% for the less represented category) these categorical covariates were not included in the full covariate model.

Conclusions:

We described the occurrence of CIPN and determined the impact of various treatment and patient characteristics on the risk of CIPN using TTE analysis. With this methodology we additionally accounted for the information about time on treatment and censored observation on risk of PN. The risk of CIPN increased with increase in administered dose and age. The model enables evaluation of the impact of treatment and patient characteristics on the risk of CIPN.

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I-61: *Dan Wright* Identifying systematic bias in model predictions

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Objectives:

An assessment of predictive performance is required to demonstrate that a model is fit for purpose and has potential utility in the intended setting. In the setting of non-repeated measures data (e.g. assessment of model-based dose predictions) we expect a linear relationship between the predicted and observed data. When plotted on an x,y plot, the predictions should cluster close to the line of identity. Deviations from the line of identity may suggest bias in the model predictions. A method for assessing predictive performance was described by Sheiner and Beal [1] where bias is estimated using mean prediction error (MPE). MPE provides a measure of the magnitude and direction of bias across the range of observed data while the 95% confidence interval (CI) provides a statistical criterion for the presence of bias. Using this method, the data are assumed to arise from a single bin. We propose that MPE will be insensitive to bias when the relationship between prediction error and the observed data displays a systematic trend over the range of the observations. The objective of this study is to illustrate a method for detecting systematically biased predictions over the range of observations.

Methods:

Overall Approach: The proposed method represents a generalised form of the MPE (single bin) approach proposed by Sheiner and Beal [1]. Here, multiple bins were created across the observed data. The method was developed and evaluated in three steps.

Observed data were binned and the slope of the MPEs vs bin was determined.

- Starting with n=2 bins, n bins of equal width were created across the x-axis.
- The mean prediction error (MPE) of each of n bins was calculated.
- The MPE value was regressed against the bin number.
- The steps above were repeated until n=the maximum number of bins.

The asymptomatic slope at infinite bins was determined.

- The slope values were regressed against the number of bins using an exponential model to determine the asymptotic slope at infinite number of bins.
- If the 95% CI of the asymptotic slope included zero, then no systematic bias was concluded.

The method was evaluated for seven scenarios, illustrating different patterns of systematic bias; (1) unbiased predictions (control), (2) linear, off-set, bias (predictions are shifted below the line of identity), (3) linear, bidirectional, bias (slope of the regression line <45 degrees), (4) non-linear, unidirectional bias at larger observations, (5) non-linear, unidirectional bias at lower observations, (6) combined off-set (linear) and unidirectional (non-linear) bias, and, (7) curvilinear, non-monotonic, bias.

All simulations were conducted in MATLAB and data sets included 50 predicted and observed doses. Random noise was simulated assuming a normal distribution with a mean of zero. A variance 0.25 was used

as this value was sufficient to provide random variability but still maintain the shape of bias. MPE (95% CI) using a single bin and the asymptotic slope (95% CI) at infinite bins were determined for each simulated scenario.

Results:

In the control scenario, both the single bin MPE and asymptotic slope method correctly specified the absence of bias. For scenario 2 (off-set bias), the MPE method identified the presence of a bias while the asymptotic slope method correctly identified that the bias was not dependent on the size of the observations. The single bin method did not identify bias in scenarios 3-6. In contrast, the asymptotic slope method correctly detected systematic bias in these scenarios, all of which were characterised by a monotonic deviation from the line of identity (scenarios 3, 4, 5, and 6). Neither method could detect curvilinear bias (scenario 7).

Conclusions:

A method for numerically detecting systematic deviation in model-predictions has been proposed. It provides an additional interpretation to the standard single bin MPE approach. The method has similarities to visualizing a LOESS regression, which is useful for visualising deviation from the line of identity, but differs in that it provides numerical and statistical quantities associated with the deviation. The method could be automated and implemented in statistics software.

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I-62: *Liviawati Wu* Population Pharmacokinetics and Dosing Simulation of JNJ-64155806 (AL-794) in Healthy Volunteers

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Objectives: To develop a nonlinear pharmacokinetic (PK) model that characterizes the exposures of ALS-033719 and ALS-033927, the active moiety and metabolite, following oral administration of a prodrug JNJ-64155806. The model was used to simulate different dosing regimens for further clinical development.

Methods: PK data were obtained from 4 phase 1 clinical studies, involving 194 healthy subjects. A total of 5767 and 5762 plasma concentrations of ALS-033719 and ALS-033927, respectively, and; 41 and 42 urine concentrations of ALS-033719 and ALS-033927, respectively, were used. Dose ranged from single dose 50-2000 mg, and twice daily 50-600 mg. The data were analyzed by a non-linear mixed effects modeling approach implemented in NONMEM V7.3.0[1]. The covariates considered were fed status, formulation, sex, race, age, weight, and selected baseline laboratory values. Although the categories of Japanese (n=6) and female (n=18) represented less than 10% of the total number of subjects, these covariates were tested because these subjects had significantly higher exposure than the rest of predominantly male subjects with other race categories. Enterohepatic circulation[2] and diurnal variation were also evaluated. Model performance was supported by diagnostic plots, standard error of parameters, evaluation of shrinkage and visual predictive checks. Dosing simulations were guided by the constraints of C_{max} below 1000 ng/mL and AUC_{12h} below 6500 ng·h/mL.

Results: The complex JNJ-64155806 pharmacokinetics was successfully described by a two-compartment model, including pre-systemic degradation in the gut, saturable absorption from gut to intestine that has circadian variations and time-varying food effects[3], transit from intestine to central compartment, glucuronidation, and renal clearance of both parent and metabolite. The glucuronidated fraction of ALS-033719 was estimated to be 96.9%, with the remaining 3.1% eliminated in the urine. The final model included Japanese and female subjects having reduced clearance terms (30-40%), food (standard and high-fat meal) and formulation (tablet vs suspension) effects on both transit absorption rate constants and maximal rate of gastric release from gut to intestine. Inter-individual variabilities for clearance of the parent, clearance of metabolite, central volume of distribution and transit absorption rate constants were 30%, 102%, 45% and 40%, respectively; with low shrinkage of 3.4%, 16.1%, 2.4% and 4.7%, respectively. Proportional residual variabilities were estimated as 35-40% for plasma and 62-64% for urine. Simulations suggested that 100 mg loading dose followed by 50 mg twice daily will meet the C_{max} and AUC criteria for the subpopulation of Japanese/women (where exposures are expected to be higher).

Conclusions: A semi-mechanistic population PK model has been developed that can adequately describe the nonlinear absorption, plasma and urine concentrations of ALS-033719 and ALS-033927 in healthy volunteers. Simulations allowed the recommendation of a dosing regimen for the clinical development of JNJ-64155806 for the indication of influenza A and B infection.

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I-63: *Gudrun Wuerthwein* Population pharmacokinetics for PEGylated asparaginase Oncaspar® in children with ALL: differences between protocol parts and predictivity

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Objectives:

The pharmacokinetics of the polyethylene glycol (PEG)-conjugated asparaginase Oncaspar® is characterized by an increase in elimination over time. An empirical transit compartment model was implemented to describe this time-dependency in pharmacokinetics (PK) [1].

Focus of our analyses were:

- to build up a covariate model
- to account for the significant differences in drug exposure between different parts of the protocol
- test the accuracy of the model (based on the PK model, individual drug exposure over the whole asparaginase therapy has to be predicted in order to correlate these data with clinical outcome and toxicity parameters).

Methods:

In paediatric acute lymphoblastic leukemia therapy (AIEOP-BFM ALL 2009; registered at www.clinicaltrials.gov as NCT0111744), two administrations of Oncaspar® (2500 U/m^2 intravenously) in induction phase (14 days interval) and one single administration in reinduction were followed by weekly monitoring of asparaginase activity. For this analysis, the starting model was the previously published non-linear mixed-effects model [1]. Besides age and sex as potential covariates, the marked difference in drug exposure between induction and reinduction was a major focus during model development (median asparaginase activity: 1. administration in induction, day 7: 882 U/L, day 14: 534 U/L; reinduction: day 7: 1445 U/L, day 14: 748 U/L).

Predictivity of the model was tested for single observations as well as for the derived PK-parameters AUC (based on integration of the model) and time over 100, 250, 500 and 1000 U/L, resp.: for patients, where all 6 drug-monitoring samples were available, 2-4 samples were excluded and then the accuracy of the predicted metrics were calculated.

Results:

The previously published transit model included 14 compartments with 4 PK-parameters: V=volume of distribution, CLP=clearance from each compartment, CLE=additional clearance from the last compartment, Q_{tr}=constant inter-compartmental clearance [1]. In a first step, the model could be simplified by replacing CLE with the transit-compartment clearance Q_{tr}.

Inclusion of covariates on CLP (68% decrease at reinduction) and Q_{tr} (60% increase at reinduction) were best to account for the differences in PK between induction and reinduction (dOFV= -1692). However, interpretation of these pronounced changes of PK-parameters on a pharmacological level seems to be difficult: CLP might be interpreted in terms of elimination by monocytes and macrophages; thus, lower elimination rates in reinduction seem to be plausible. However, the transit-clearance Q_{tr} might reflect the rate of de-PEGylation of the molecule in vivo; here, changes observed in different protocol parts can only be postulated. Other pharmacologically more plausible attempts to model these differences resulted in less pronounced improvement of the model. Unsymmetrical distribution of ETAs for interoccasion variabilities on CLP and V as well as VPCs stratified on each Oncaspar® administration further indicated a slight underprediction of observed data for the 2nd induction administration. Thus, additional covariates on CLP and V for the 2nd induction administration were included in the model (dOFV= -214). Sex (dOFV= -22.1) and age (dOFV= -24.5) as additional covariates further improved the model.

The accuracy for AUC or time over predefined asparaginase activities were superior to the accuracy for individual observations: The percentage of individuals within a 10% error range from true parameters ranging from 60-100 % for AUC, 85-100 % for time over 100 U/L and 25-31 % for individual observations for the different scenarios tested (percentage of individuals within a 20 % error range: 87-100 % for AUC, 96-100 % for time over 100 U/L and 47-52 % for individual observations).

Conclusions:

Besides covariates for induction vs. reinduction, the PK model accounts for slight accumulation after subsequent Oncaspar® administrations. Test of accuracy demonstrates that derived PK-parameters AUC or time over predefined asparaginase activities are more promising parameters than predictions of individual asparaginase activities for further PK-PD correlations.

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I-64: *Li Xia* Population pharmacokinetics of ciprofloxacin in critically ill patients-a covariate analysis

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Objective:

For critically ill patients, physiological changes result in altered ciprofloxacin pharmacokinetics, possibly causing inadequate drug exposure. We aimed to identify those covariates which are the best predictors of ciprofloxacin pharmacokinetics concerning kidney and liver function in ICU patients.

Method:

A population pharmacokinetic model was built based on 444 ciprofloxacin plasma concentrations collected on four consecutive days from 15 critically ill patients with severe infections receiving standard dosing of ciprofloxacin in a prospective observational study. Relationships between ciprofloxacin clearance and renal, hepatic and biometric covariates were evaluated independently on study days 1 to 4 to assess whether a covariate was consistently related to clearance throughout the treatment course. For covariates which reduced the AIC, the stability of the relationship was confirmed by evaluating the 95% confidence intervals (CI) of the respective covariate parameters as obtained from a bootstrap with 1,000 samples [1]. A covariate was introduced into the model if the related 95% CIs did not include zero on at least three out of four treatment days. Subsequently, the relevance of covariates was assessed by evaluating the magnitude of change in clearance compared to the typical population clearance that was explained by the covariate. The identified covariates were then combined in the final covariate model.

Result:

A two-compartment model with linear elimination and a combined error model appropriately described the pharmacokinetics of ciprofloxacin. Clearance and central volume of distribution increased from the first (16.2 [13.4 – 19.7] L/h and 24.2 [13.9-36.4] L) to the fourth (20.9 [17.8 – 25.8] L/h and 33.5 [21.3-48.8] L) study day (median [95% CI] from bootstrap). The peripheral volume and the inter-compartmental clearance were 83.2 (74.1-94.8) L and 71.2 (46.2-93.9) L/h, respectively (median and 95% CI). Bilirubin (Eq. 1), age (Eq. 2), and sex (Eq. 3) were identified as covariates consistently related to clearance throughout the treatment course. In the final covariate model, the unexplained inter-individual variability of clearance was reduced from 55% (base model) to 22%.

Eq. 1 $CL_{BILI}=(BILI/1.85)^{**}\theta_{effect\ of\ BILI}$

Eq. 2 $CL_{AGE}=1+(49-AGE)*\theta_{effect\ of\ AGE}$

Eq. 3 $CL_{SEX}=1+(1-SEX)*\theta_{effect\ of\ SEX}$

Eq. 4 $CL=\theta_{CL} * CL_{BILI}*CL_{AGE}*CL_{SEX}$

Equation 1 to 4, covariate equations describing the identified relationships between bilirubin (BILI, mg/dL), age (AGE, years), sex (SEX, 1 = male) and ciprofloxacin clearance. The effect of total plasma bilirubin concentration on the clearance $\theta_{\text{effect of BILI}}$ was -0.25(-0.374- -0.138), the effect of age on the clearance $\theta_{\text{effect of AGE}}$ was 0.0156(0.0021-0.0208), and the effect of sex on the clearance $\theta_{\text{effect of SEX}}$ was -0.413(-0.559- -0.214).

Conclusion:

According to our research, age, sex, and bilirubin might be more relevant to predict ciprofloxacin pharmacokinetics in critically ill patients, rather than creatinine clearance calculated by the Cockcroft-Gault equation[2] as described previously [3].

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I-65: *Feifan Xie* A model-based analysis of the kinetics of leukocytes in stage III ovarian cancer patients treated with neo-adjuvant chemotherapy, cytoreductive surgery and cisplatin-based intraperitoneal chemoperfusion

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Objectives: One of the well-known side effects of cisplatin, a chemotherapeutic agent used since the 1970s, is haematological toxicity[1]. However, little is known on the quantitative relationship between the pharmacokinetics and the haematological toxicity. The goal of this study is to develop a pharmacokinetic-pharmacodynamic (PKPD) model that explains the time course of leukocytes in stage III ovarian cancer patients. Ideally, this model should account for the residual myelosuppressive effects of prior doses of neo-adjuvant systemic chemotherapy (carboplatin and paclitaxel), the transient leucocytosis induced by cytoreductive surgery (CRS), and the myelosuppressive effect of cisplatin-based intraperitoneal chemoperfusion.

Methods: In a randomized design, 24 patients received CRS followed by a normothermic (37°C) or hyperthermic (41°C) intraperitoneal chemoperfusion ((H)IPEC) with a cisplatin dose of 75 or 120 mg/m2. 19 out of 24 patients had extensive tumor dissemination and received 3-4 courses of systemic carboplatin and paclitaxel based neo-adjuvant chemotherapy before CRS and (H)IPEC. A minimal waiting period of at least 1.5 weeks was respected between the last dose of neo-adjuvant chemotherapy and the date of CRS and (H)IPEC. Peritoneal perfusate (n=70; range: 2–3 per patient) and venous blood samples (n=144; range: 5–8 per patient) were collected up to 1.5 h and 24 h respectively after the start of 90 min cisplatin-based (H)IPEC. The intact cisplatin was measured using a validated UHPLC-MS/MS method[2]. Leukocytes (n=236; range: 5–15 per patient) were measured before CRS and up to 14 days post (H)IPEC. The data were analysed using the first-order conditional estimation (FOCE) method with interaction implemented in NONMEM®(version 7.3; Icon Development Solutions, Hanover, MD, USA). A sequential approach was followed where first a population pharmacokinetic model was constructed for intact cisplatin. Subsequently, the resulting individual predicted concentrations were used as a driving force for the leukocyte counts.

Results: A two-compartment model with first-order absorption and elimination was shown to adequately describe intact cisplatin pharmacokinetics. The PKPD model was based on a previously described semi-physiological chemotherapy-induced myelosuppression model[3]. The reported myelosuppression model was extended by adding a deposit compartment representing the stored mature leukocytes within the bone marrow sinusoids. A linear cisplatin concentration-effect on the proliferation rate of the leukocytes best described their counts. A feedback loop on the proliferation from the circulating leukocytes was incorporated in order to describe the rebound of leukocytes compared with the baseline value. CRS was assumed to initialize the mobilization of leukocytes from the deposit compartment to the circulating compartment[4] and increased the mitosis rate of proliferative cells[5]. The mobilization of leukocytes was modelled as a first-order release from the estimated initial amount of cells in the deposit compartment. The CRS effect on the proliferation rate was modelled by a stimulatory function resulting from the surgery and exponentially declining over time. The residual myelosuppressive effect of the neo-adjuvant chemotherapy was added to ascertain a physiologically reasonable model prediction of baseline leukocyte

counts once all treatment effects had worn out. Diagnostic plots and visual predictive checks demonstrated a good agreement of model predictions with the observed data. The model also allows for reasonable extrapolations outside the range of data measured.

Conclusions: A leukocyte model was developed to simultaneously account for the residual myelosuppressive effect of neo-adjuvant chemotherapy, the transient leucocytosis response induced by CRS, and the myelosuppressive effect of cisplatin-based (H)IPEC. The PKPD model demonstrates that leucocytosis and leucopenia were reversible and short-lasting following CRS and cisplatin based (H)IPEC. In the absence of other cisplatin-induced side effects, higher cisplatin (H)IPEC doses could be considered without significantly raising the risk of major haematological toxicities.

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I-66: *James Yates* Structural Identifiability for Mathematical Pharmacology: Models of myelosuppression

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Objectives: Structural identifiability is an often overlooked, but essential, prerequisite to the experimental design stage. The property of identifiability arises in the validation process because experiments for data collection give rise to an input-output behaviour for the model, which defines how external inputs (perturbations) arise in the model and what functions of the model variables correspond to directly measured species. Structural identifiability considers the uniqueness of the unknown parameters with respect to this input-output behaviour, and is fundamental since estimates for unidentifiable parameters are effectively meaningless. Moreover, the presence of unidentifiable parameters can result in errors in predictions or inferences made from the model. The application of structural identifiability analysis to models of myelosuppression is used to demonstrate the importance of its consideration. Secondly, the consistency of system parameter estimates for the Friberg et al paper was investigated via a meta-analysis of the literature.

Methods: The model first published by Friberg et al [1] and 3 modifications, Bender et al [2], Mangas-sanjuan et al [3] and Quartino et al [4], were investigated. Structural identifiability analysis was carried out using the observable normal form approach [5] and the IdentifiabilityAnalysis [6] package in Mathematica. Symbolic computation was carried out in Mathematica and Maple. Consistency of parameter estimates for the Friberg et al model were visualised using Galbraith plots [7]. In this plot the reported parameter estimate divided by the reported standard error (SE) is plotted on the ordinate versus 1/SE. This plot serves two purposes: Firstly, if estimates are consistent given their precision, points will lie on a straight line. Secondly, the estimates with greater precision will aggregate away from the origin and so the slope of the regression will be the mean of the parameter estimates weighted by their precision.

Results: Assuming that the model is started at baseline from pre-treatment steady state, all four models are structurally globally identifiable under certain conditions. For Friberg et al this is under the assumption that the rates of proliferation and maturation are numerically equal ($k_{prol} = k_{tr}$). This is also the same for Bender et al. For Mangas-sanjuan et al the model is similarly structurally globally identifiable for the case $k_{prol} = F_{prol}\, k_{tr} = F_{prol}\, k_{circ}$, where F_{prol} is the fraction of proliferating cells entering maturation. Finally, if GCSF concentrations are not observed then Quartino et al is structurally globally identifiable only by reparametrizing the model so that the G-CSF state has a steady state of 1. The meta-analysis of reported parameter estimates for the Friberg et al model demonstrates striking consistency of estimates across reports in the literature (mean maturation time of 109 hours, baseline circulating neutrophils of 5.15×10^9/L and feedback power of 0.148) and demonstrates the application of a structurally identifiable model that can separate system and drug specific effects.

Conclusions: It is shown that, under certain assumptions, these models are structural identifiable and so drug and system specific parameters can truly be separated. Further it is shown via a meta-analysis of the literature that because of this the reported system parameter estimates for the “Friberg” or “Uppsala” model are consistent in the literature.

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I-67: *Jinqiu Yin* Optimizing treatment of cephalosporin-resistant pneumococcal meningitis

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Introduction:

Bacterial meningitis is a life-threatening condition associated with a high mortality. In adults, Streptococcus pneumoniae remains the most common cause for bacterial meningitis[1]. Typically antibiotic treatment of pneumococcal meningitis is based on treatment with penicillin and third-generation cephalosporins[2]. However, resistance to penicillin and cephalosporins is increasing[3] in which case vancomycin in combination with rifampicin or cefotaxime is recommended[2].

The blood-brain barrier (BBB) can impact exposure of antibiotics to the central nervous system (CNS)[4]. Consequently, the rate and extent of drug distribution into the CNS needs to be accounted when optimizing antibiotic treatments of bacterial meningitis. Furthermore, predicting antibiotic exposure in the brain may be relevant in preventing CNS-associated adverse drug reaction[5,6]. Various dose regimens to treat resistant bacterial meningitis have been proposed, including the continuous intravenous administration of vancomycin[7] and intrathecal injection of vancomycin[8]. To further optimize these dose regimens of meningitis in specific patient populations, quantitative characterization of the kinetics of CNS exposure as well as bacterial growth kinetics should be considered.

Objectives:

We aim to develop a pharmacodynamic model to characterize to exposure-response kinetics of Streptococcus pneumoniae to vancomycin that can be coupled to a previously developed CNS PBPK model in order to optimize vancomycin dose regimens for S. Pneumoniae associated bacterial meningitis[9,10]. The current analysis focuses on the development of the development of the pharmacodynamic model.

Methods:

Experimental data: We extracted time-kill data from previous publications featuring 7 bacterial strains[11-13]. The studies described static in vitro experiments with S. Pneumoniae with various concentrations of vancomycin.
Model development: We used a nonlinear mixed effect modeling to analyze the in vitro time kill data. We evaluated natural bacterial growth both as non-capacity limited growth with a net growth constant, and as capacity limited growth using a logistic growth function. Both the incorporation of a persistent and tolerant sub-population was evaluated. The drug effect was evaluated as a linear slope and as an Emax function. Additionally, inclusion of random effects for variability between time kill time courses and strains (ISV) was evaluated for all relevant parameters. The developed time kill model was subsequently linked to the previously developed CNS PBPK model to allow for treatment optimization of vancomycin.

Results:

The developed time kill model contained two sub-populations of bacteria, one non-growing non-drug sensitive persistent population (BP) and one drug-sensitive (BS) with growth following a logistic function modeled with a net growth constant (Knet) and a capacity limiting term (Bmax). The data did not support a more mechanistically plausible drug tolerant sub-population. The number of Bs and Bp at start of experiment was estimated as BS0 and BP0 respectively. The drug effect was included as an Emax model. Parameter estimates were: BS0 3.35 log CFU/mL (RSE 3%, ISV 100%), Knet 0.445 h-1 (RSE 14%), Bmax 11.2 log CFU/mL (RSE 3%, ISV 21%), Emax 4.87 (RSE 23%, ISV 100%), EC50 0.731 mg/L (RSE 34%, ISV 39%).

Conclusions:

We quantified the time-kill dynamics S. pneumonia to vancomycin which allowed integration with a previously published model of CNS pharmacokinetics, resulting in a strong modeling framework to optimize S. pneumoniae meningitis. In future, the work will be further extended with de novo time kill data and combination treatments.

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I-68: *Gunnar Yngman* Linearization of full random effects modeling (FREM) for time-efficient automatic covariate assessment

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Objectives:

Full Random Effects Modeling (FREM) is a methodology for covariate modeling whereupon a covariate set of interest is pre-specified before all covariate-parameter effects are estimated simultaneously (through parameter-covariate covariance estimation). It has been used with NONMEM, is implemented in PsN [1] and the technique and motivation has been suggested and described before [2,3,4].

Linearization is another methodology implemented in PsN which allows automatic linearization of a NONMEM model around the estimated typical population parameters, leaving only the random effects of the model to be estimated (conditional on the typical values) [5]. It has been shown to enable fast and relatively unbiased approximations of the non-linear model in many situations where the typical values are not expected to change, such as during covariate modeling [6]. Linearization is utilized by default in the new QA PsN script to speed up the entire procedure, of which FREM constitutes a vital component [7].

The aim of this investigation was to explore the suitability of linearization as a methodology for FREM in the context of automatic model assesement, with an implementation where the base model is linearized before the full PsN FREM functionality is executed.

Methods:

To investigate the appropriateness of linearized FREM 33 in-house NONMEM models were estimated with and without linearization through the QA tool, without manual tweaking. Of the models which terminated to an objective function value, linear and non-linear FREM results were compared with respect to univariate coefficients, estimation time and uncertainty characterization. The coefficients were standardized by the standard deviation of the covariates to reduce the importance of strength of relation. Since linearization is meant to be used as an approximation of the original non-linear models, the error of linear FREM was investigated with respect to the non-linear base case.

Results:

14 of the 33 models successfully produced an OFV with both linear and non-linear full FREM in QA, from which 239+239 univariate coefficients could be retrieved. Estimation times spanned a large range (0.38 s to 29 min). The median estimation duration of final full linear and non-linear FREM models were 6 and 205 seconds, respectively. On average, the linear variant exhibited 83 times faster execution. The mean absolute univariate coefficient size was 0.515 and 0.428 for linear and non-linear models, with a mean absolute error of 0.232 (54.3% of mean non-linear coefficient size). No clear bias was observed. Only 3 models shared a successful covariance step. However, the success rate was significantly higher for linear (9) than non-linear (4) executions.

Conclusions:

Linearized FREM shows slight but relatively small differences of no detectable bias, in terms of estimated univariate covariate-parameter relations, to the non-linear base models in the automated QA context. In addition linearization provides aid in uncertainty characterization in NONMEM. The technique shows promise as a time-efficient approximation in automatic model assessment.

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I-69: *Jurij Zdovc* The expression of ABCB1 gene influences the PK of rivaroxaban – a PK/PD study in patients with the total hip or knee arthroplasty

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Objectives: Rivaroxaban is a relatively recent, oral, direct Factor Xa inhibitor. In patients undergoing hip or knee replacement surgery it is indicated for prevention of deep vein thrombosis which may lead to pulmonary embolism [1]. After administration, approximately two thirds of the dose are metabolized in liver, from which one half is then excreted via kidneys and the other half via hepatobiliary route. One third of the administered dose is excreted unchanged via kidneys, most of it through renal secretion [2]. The in-vitro and in-vivo studies demonstrate that the transporters involved in the process of renal secretion are the protein ABCB1, also known as P-glycoprotein (P-gp) and the Breast cancer resistance protein. As a consequence, rivaroxaban is advised not to be taken concomitantly with strong P-gp inducers or inhibitors [3–5]. Our study aims to assess the population PK and PD of rivaroxaban in patients undergoing the total hip or knee replacement. We aim to evaluate the influence of the *ABCB1* gene expression and two single nucleotide polymorphisms (SNP) on the PK and PD of rivaroxaban.

Methods: There were 17 patients included in the study and all of them were scheduled for their first total hip or knee replacement. Before the surgery we performed the polymorphism genotyping and the *ABCB1* gene expression assay. 6 h after the surgery the patients started with the thromboprophylactic therapy, which consisted of 10 mg of rivaroxaban per 24h, on an empty stomach. Subsequently we measured the concentration of rivaroxaban in plasma and performed the tests of coagulation. A total of 82 plasma concentration-time points were used to develop the PK model. Some of the measurements were below the limit of quantification (BQL, < 1 ng/mL), so we used the M3 estimation method, together with the Laplacian estimation. A one-compartment model with first-order absorption was fitted to the logarithmically transformed plasma concentrations. The first order conditional estimation with interaction was used as an estimation method for the parameters. We tested the influence of the following covariates: age, sex, genetic polymorphisms on the gene *ABCB1* – rs10445642 and rs4148738, body mass index, smoking, glomerular filtration, concomitant medication and the *ABCB1* expression.

Results: A simple one-compartment PK model with first order absorption best fitted our data. Due to the difficulties in the convergence we transformed the data to the logarithmic scale. The ka was estimated at 0.147 h^{-1}(with a relative standard error of 14.3 %), the oral Cl for the person with the gene expression of 1.25 was 6.12 L/h (15.8 %) and the volume of distribution was estimated to 96.8 L (13.1 %). The typical value of the parameter relating the gene expression and Cl was 0.817 (28.8 %). We were able to estimate the inter-individual variability on ka and Cl, which were 204 % (8.63 %) and 70.9 % (13.6 %), respectively. The residual variability was proportional and estimated at 59.6 % (12.7 %). During the covariate modeling the expression of *ABCB1* gene entered the final model and the final equation for Cl was $Cl = 6.12*(ABCB1/1.25)^{0.817}$. From this relation we observed that the Cl of rivaroxaban decreases with a lower *ABCB1* gene expression, which corresponds with the fact that rivaroxaban is the substrate for the P-gp. In almost all subjects (16 out of 17) the gene expression decreased after the surgery and the Cl lowered accordingly. With respect to the PD, prothrombin time (PT) and partial thromboplastin time (aPTT) were both linearly associated to the natural logarithm of the rivaroxaban concentrations in plasma. The intercept PT and aPTT were estimated to the 12.8 s (4.48 %) and 32.9 s (4.08 %), respectively. The residual error was modeled with additive type of error and proportional type of error in the PT and aPTT models, respectively.

Conclusions: The study showed that the one-compartment PK model with the first order absorption is a suitable model to describe the PK of rivaroxaban. We confirmed the correlation between the *ABCB1* gene expression and the Cl of rivaroxaban, which corresponds to the fact that the rivaroxaban is a P-gp substrate. The analysis also indicated that the PT and aPTT increase with the increased dose of rivaroxaban and are good indicators of PD. An interesting finding was also that the *ABCB1* gene expression decreased after the orthopedic surgery. We were not able to explain that phenomenon and further research is needed to assess and explain the mechanism.

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I-70: *Nan Zhang* Creation of Pharmacometric Framework to Evaluate Clinical Trial Data on Predictive Biomarkers

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Objectives:

The identification of biomarkers that can predict subjects to respond to a therapy is an important objective of what is popularly called “precision medicine”. Some genetic markers, particularly for mutational drivers of tumor growth, have been used to provide a relatively straightforward rationale for therapy response or lack thereof due to their dichotomous nature. However, pathway activation markers as predictors of response to therapy tend to be more complex for various reasons. Qualifying these biomarkers as predictive and fit for purpose during early phase development presents many challenges from a data analysis point of view, including presence of data from sub-optimally effective doses tested during phase 1 and 2, variation of placebo effect as disease severity changes, and cut-point determination for optimal separation of effect. So far, all assessment of the value of biomarkers has only been done using pair-wise comparison of the effect at a specific time point in the biomarker-high vs biomarker-low groups [1]. Therefore, we developed a pharmacometric framework for the analysis of biomarker data to assess whether a complementary longitudinal data analysis using pharmacokinetic/pharmacodynamic (PK/PD) and biomarker modelling could add benefit in the interpretation of predictive biomarker data, as well as to evaluate therapeutic drug monitoring and adaptive phase 3 design.

Methods:

The simulations in this work were performed in context of standard Phase 2B design for a biological therapy for the treatment of inflammatory bowel disease and it was based on two different dose ranges, **A**) 300 mg, 1000 mg, 2000 mg (all above ED50) or placebo, and **B**) 50 mg, 300 mg, 2000 mg (all doses at ED50 and above) or placebo, and three different study settings: at drug range **A** or **B**, a placebo-controlled parallel study with biomarker effect on drug effect (Setting 1 and 2), or on placebo effect (Setting 3 and 4), or on both drug effect and placebo effect (Setting 5 and 6). PK of this virtue drug is described using a linear 2-compartment model, whereas its PD is described as an indirect inhibition. The biomarker effect is implemented as a function on drug effect (Emax) and/or Placebo using range of functions including Emax model with g of 1.5, 2, 3, 5, or 50, linear model and dichotomous model. The biomarker covariate is sampled using the mean and standard deviation of C-reactive protein level from a clinical dataset following a log normal distribution.

In each setting, we assess the power of identifying biomarker effect using modelling versus standard statistical approaches (group comparison) at end of the study. Stochastic simulations and estimations were used to compute model parameter precision and accuracy as well as to power.

Results:

All studied scenarios with biomarker effect on model parameters had a power more than 80% for the biomarker detection except the linear biomarker effect model when biomarker effect is on Emax and/or placebo effect and the alternative model is drug effect only model or when both Emax and placebo effect is dependent on biomarker level and the alternative model is biomarker-dependent drug effect model. Overall, the order of power for detecting such an effect is linear model < Emax model (g=1.5) < Emax model (g=2) < Emax model (g=3) ≈ Emax model (g=5) ≈ Emax model (g=50). The power for dichotomous model for both two dose ranges is either between that of Emax models and linear model or above that of all Emax models depending on biomarker effect relationship.

Model parameters could be estimated with reasonable precision and bias with small sample sizes, except the precision of EC50, placebo effect and its inter-individual variability, and gamma, as well as the bias of PD residual error and placebo effect.

Additionally, the power for detecting biomarker effect using statistical analysis is not consistent with that using PK/PD modeling method, and the power differs depending on the cutoff value and doses.

Conclusions:

A framework has been developed for analyzing continuous predictive biomarker. Multiple factors, such as biomarker-dependent drug effect and/or placebo effect and dose ranges, have been evaluated in affecting the power of detecting biomarker effect. This platform has improved the ability to characterize both exposure-response and the predictive value of the biomarker by simultaneous modeling of PK/PD data from all dose cohorts while including a predictive biomarker covariate.

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I-71: *Ying Zhang* Exposure–Response Model and Development of a Shiny App of Subcutaneous C1-Inhibitor Concentrate to Estimate the Risk of Attacks in Patients with Hereditary Angioedema (HAE)

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Objectives: Hereditary angioedema (HAE) is a rare, debilitating, and potentially life-threatening, autosomal dominant genetic disease caused by a deficiency in functional C1 esterase inhibitor (C1-INH). Long-term prophylactic subcutaneous administration of C1-INH is an established treatment option for patients with HAE. An analysis was conducted to assess the relationship between C1-INH functional activity levels (C1-INH(f)) and the risk of a HAE attack in patients with HAE. A Shiny application (app) was developed to generate and demonstrate the simulation results with various dosing scenarios.

Methods: A population pharmacokinetics (POPPK) analysis was performed using data from the Phase 1 to Phase 3 clinical studies of treatment with C1-INH (IV) or C1-INH (SC) treatment (total 2103 samples). A repeated time-to-event model was used to characterize the timing and frequency of attacks as a function of C1-INH(f) that enabled the C1-INH(f) to be directly related to the HAE attack event using 90 subjects from the Phase 3 COMPACT study experienced 1191 attacks and 234 censored events. Parametric model development assessed three main components; a background effect, a non-drug effect (e.g. time effect), and a C1-INH (SC) effect, which allowed for informative use of the changes in C1-INH(f). C1-INH(f) covariate effects were evaluated using the Wald's approximation method procedure. The final model was used to simulate the absolute hazard of attacks over a wide range of C1-INH(f) values (20–120%). The hazard ratio was computed using the geometric mean of observed baseline C1-INH(f) as the reference (25.4%), compared to C1-INH(f) ranging from 25.4% to 120%. An interactive Shiny app was created using R packages to simulate and demonstrate the simulation results for C1-INH(f) and the hazard risk at various dosing scenarios.

Results: The C1-INH(f) following administration of C1-INH (SC) was adequately described by a linear one-compartment model with first-order absorption and first-order elimination, with inter-individual variability on all the parameters. The population pharmacokinetic model found body weight to be a significant covariate on clearance. The PK/PD model demonstrated a strong exposure-response (E-R) relationship, with increasing C1-INH(f) decreasing the risk of experiencing an HAE attack. The final model included 2 components, a baseline hazard and a non-linear drug effect. Age had a significant effect on the E-R relationship in terms of a higher risk of HAE attack for a given baseline plasma C1-INH(f) level. The response to treatment C1-INH on the risk of HAE was independent of age. The mean trough C1-INH(f) after subcutaneous administration was predicted to yield a 70% reduction in the relative risk of an HAE attack after 40 IU/kg dosing and an 81% reduction after 60 IU/kg dosing. Simulations based on the E-R model predicted that higher C1-INH(f) significantly lowers the risk for HAE attacks in a greater proportion of patients with maximal effect occurring near normal C1-INH(f). The Shiny app can perform the simulation efficiently and demonstrate the simulation results with the interactive and dynamic display.

Conclusions: Simulations based on data from the COMPACT program suggest that the prevention of HAE attacks is maximized when C1-INH(f) are restored to the normal range (> 70%).

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I-72: *Fan Zhang* Structural and Practical Considerations in the Development of a Parent-metabolite Model

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Introduction:

Issues often exist in parameter estimation of pharmacokinetic (PK) models for a parent drug and its metabolites. The model could be structurally non-identifiable even with perfect data, if the data for intravenous PK, or the metabolites alone PK, or the fractions of parent drug to metabolites are not available. With structurally identifiable model, real-life conditions may still cause the model parameters to be non-estimable.

To illustrate these points, we present a case of PK modeling for Wellbutrin XL (bupropion hydrochloride extended-release tablet). Bupropion XL is well absorbed and only small proportion of an orally administered dose reaches the systemic circulation intact due to high first-pass metabolism. Its three main active metabolites, hydroxybupropion, erythrohydrobupropion and threohydrobupropion, have been identified. Many existing PK studies for bupropion have been conducted over the past decades; however, their analyses have not yet provided enough insight into the conversion of bupropion to its 3 metabolites, and could not serve as a basis for better understanding of the underlying mechanism and for guiding the dose adjustment as a later goal.

Objectives:

To describe the PK of bupropion XL and its 3 active metabolites, and more importantly, to use this post hoc analysis as an example to discuss some common issues for modeling PK concentration data for parent compound and its metabolites when the drug was administered only orally.

Methods:

The data used for model building was from a GSK funded Phase I, open-label study (NCT02698553) conducted in healthy Chinese subjects. In this study, for safety consideration, dose titration strategy was used. 16 subjects received bupropion XL 150 mg once daily (QD) for 5 days, and then the dose was titrated to 300 mg QD from Day 6 to Day 14. Blood samples were collected pre-dose and Day 1, 5, 6, and 14-19. Three different model structures were investigated:

1. first-pass effect not considered, the parent drug was either eliminated from the system or transformed into the 3 metabolites;
2. first-pass effect considered, the dose enters simultaneously into the parent and metabolite compartments;
3. first-pass effect considered, a dose apportionment was assigned independent of absorption rates with a fraction of dose leading to the parent, and fractions leading to the 3 metabolites as hypothetical metabolite absorption compartments prior to reaching the circulation.

The structural identifiability of these models was analyzed using Laplace transformation. Concentration data of bupropion and metabolites were simultaneously fitted using ADVAN5 and FOCE-I methods.

Results:

From the structural identifiability analysis in Model 1, the parameter ka, CLp/F, Q/F, V2/F and V3/F can be globally identified, while in Model 2, none of the parameters can be identified. In Model 3, only the absorption rate constants for the parent and all the metabolites (ka, ka4-ka6) can be identified. Model 3 was selected as final model based on mechanism and model performance. PK was adequately described for the parent drug by a two-compartment model with first-order absorption and linear elimination plus lag time, and for the metabolites by one-compartment models considering first-pass effects and systemic transformations. To have a structural identifiable model, the fractions of the parent converting to metabolites within circulation and the fractions of the parent and metabolites reaching circulation after absorption should be fixed. Those fractions were fixed to the proportions determined from the observed peak molar concentrations (Cmax) of the parent and metabolites (12.84%, 59.52%, 23.81%, and 3.83% for bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, respectively), which reflected the initial pre-systemic elimination, subsequent absorption and metabolism of bupropion.

Conclusions:

A population PK model was developed for bupropion and its three active metabolites from the study conducted in Chinese healthy volunteer. We believe a proper balance between complexity of mechanism and amount of data has to be reached for modeling parent-metabolite data.

I-73: *Xiaoyan Zhang* Population pharmacokinetic/pharmacodynamic modeling of plasma lyso-sphingomyelin response to enzyme replacement therapy olipudase alfa in patients with acid sphingomyelinase deficiency

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Background: Olipudase alfa (recombinant human acid sphingomyelinase (rhASM)) is an intravenous (IV) enzyme replacement therapy under investigation for the treatment of nonneurological manifestations of acid sphingomyelinase deficiency (ASMD), historically known as Niemann-Pick disease types A and B. ASMD is a rare lysosomal storage disorder resulting in the accumulation of sphingomyelin in multiple organs of the body due to the deficiency of ASM, and is associated with significant morbidity and mortality affecting both adults and pediatrics. To date, there are no approved etiologic-specific treatments for ASMD. Results of a Phase 1a study led to an intra-patient dose-escalation strategy, which the slow catabolism of the accumulated sphingomyelin, the less production of ceramide (and its downstream derivatives) associated with adverse drug reactions, enabled the achievement of higher target doses levels. The results of a Phase 1b study using the dose escalation strategy showed a favorable safety profile as well as clinically relevant improvements in adult ASMD patients including: 1) reduction in organomegaly, 2) improvement of pulmonary function and 3) improvement in lipid profile. Lyso-sphingomyelin (lyso-SPM) is a secondary catabolite of sphingomyelin. Plasma lyso-SPM level is often substantially increased in ASMD patients and may be a useful biomarker for monitoring treatment outcomes. Plasma lyso-SPM levels continuously decreased over the course of dose escalation in the Phase 1b study, reflecting a decrease in the accumulation of sphingomyelin with treatment.

Objectives: The current analysis aimed to develop a population pharmacokinetic/ pharmacodynamics (popPK/PD) model to characterize the exposure-response effect of olipudase alfa on the time course of plasma lyso-SPM in adult ASMD patients.

Methods: The lyso-SPM popPK/PD model was developed with PK data from 11 adult patients receiving single doses (no intra-patient dose escalation) of olipudase alfa ranging from 0.03 to 1 mg/kg in a Phase 1a study, and with PK and lyso-SPM data from 5 adult patients (4 of whom also participated in the Phase 1a study) following intra-patient dose-escalation from 0.1 to 3.0 mg/kg in a Phase 1b study (all patients reaching the target dose of 3.0 mg/kg). A sequential modeling approach was applied using NONMEM software: a population PK model was developed first to describe plasma olipudase alfa concentration-time profiles, followed by popPK/PD model development. Model-predicted individual olipudase alfa concentrations were used to develop a popPK/PD model for plasma lyso-SPM over time in adult ASMD patients. The performance of the final popPK/PD model was evaluated by visual predictive checks.

Results: The PK of olipudase alfa was adequately described by a two compartment PK model with parallel linear and nonlinear Michaelis-Menten pharmacokinetic elimination. The estimated key PK parameters are: linear clearance of 0.372 L/h, steady-state volume of distribution of 11.3 L. Body weight was identified as a covariate on both clearance and volume which supported body weight based dosing regimen.The time course of plasma lyso-SPM change was best described by a modified indirect response model with a time-varying production rate, whereas the model-predicted olipudase alfa concentrations (PK) drove the dose-

dependent inhibition of lyso-SPM, attributing to both short-term production inhibition of lyso-SPM and long-term decrease in pre-infusion baseline. The estimated key PD parameters are: Lyso-SPM degradation rate constant of 0.0431 day^{-1} and IC50 of 2.75 ng/ml.The correlation between lyso-SPM and clinical efficacy endpoints is being investigated to further enable the utility of this model to provide the link between PK, PD and clinical endpoints.

Conclusions: A population PK/PD model has been developed to characterize the time course of plasma lyso-SPM responses in adult ASMD patients following olipudase alfa treatment. Further optimization of the model is ongoing as more data becomes available. This model will serve as a critical tool to support the extrapolation of drug efficacy from adult to pediatric patients.

I-74: *Li Zhang* Mechanism-based Population PK/PD modeling of T lymphocytes Depletion and Repopulation Following Treatment with anti-CD52 Antibody GLD52 in Patients with Progressive Multiple Sclerosis

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Objectives : GLD52 (GZ402668) is a humanized IgG1 monoclonal antibody that binds to human cluster of differentiation 52 (CD52) and induces lymphocyte depletion through antibody dependent cellular cytolysis (ADCC) and complement-dependent cytolysis (CDC)[1]. This analysis aimed to: 1) develop a mechanism-based population PK/PD (Pop PK/PD) model to quantitatively describe the time profile of T lymphocytes depletion and repopulation in progressive multiple sclerosis (MS) patients follow GLD52 treatment; and 2) assess exposure-response (E-R) relationship in support of GLD52 dose selection for Phase 3 studies.

Methods : The Pop PK/PD model was developed based upon GLD52 serum concentration and total T lymphocytes from 33 patients with progressive MS from a Phase 1, first-in-human, ascending single intravenous (IV) and subcutaneous (SC) dose study (NCT02282826). The time course of GLD52 E-R relationship was described by a mechanism-based Pop PK/PD model with direct and indirect treatment effect on T lymphocytes dynamics (depletion and repopulation). The validation of the final model was performed using visual predictive checks. Clinical trial simulation (CTS) was conducted using the Pop PK/PD model to predict the extent of T lymphocytes depletion to support the selection of dose for Phase 3 studies.

Results : GLD52 elicited rapid and dose-dependent T lymphocytes depletion in the first month followed by slow repopulation. The median T lymphocytes decreased > 90% from baseline to Month 1 in the highest IV cohort and 2 highest SC dose cohorts. Lower dose showed incomplete depletion and earlier recovery of T lymphocytes. The PK of GLD52 was best described by a 2-compartment model with first order absorption and linear elimination, with typical clearance and steady-state volume of distribution of 0.66 L/day and 8.96 L, respectively. The depletion of T lymphocytes was directly stimulated by GLD52 systemic concentration with an Emax function to mimic the GLD52-elicited T lymphocytes lysis via either ADCC or CDC. The migration of T lymphocytes into circulating blood was indirectly inhibited by GLD52 via proportional suppression. Moreover, a feedback regulation was added to mimic the slow repopulation of T lymphocytes in progressive MS patients after GLD52 treatment. T lymphocytes migration time was estimated as 2.44 days, which was within the literature reported time window of lymphocytes trafficking in humans[2]. CTS revealed that full treatment courses with the highest SC dose would result in T lymphocytes depletion that was similar in extent to those observed for another anti-CD52 monoclonal antibody alemtuzumab in MS patients.

Conclusion: The time course of depletion and repopulation of T lymphocytes following GLD52 treatment in progressive MS patients was successfully characterized by a mechanism-based Pop PK/PD model. Full treatment courses of GLD52 administered by SC injection were predicted to elicit T lymphocytes depletion comparable to alemtuzumab in MS patients.

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I-75: *Chenyan Zhao* Quantification and prediction of the combined effect of minocycline and polymyxin B on multidrug-resistant Klebsiella pneumoniae

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Objectives: The increasing prevalence of refractory multidrug resistant bacteria calls for new approaches to suggest effective antibiotic combination therapies. The combined effect of minocycline (MIN) plus polymyxin B (PMB) was identified to be promising in our previous screening procedure [1] and was thus selected for *in vitro* static time-kill studies (TKS) to further evaluate the effectiveness. To characterize the observed TKS data and quantify the drug interaction effect, we aimed to develop an *in silico* semi-mechanistic pharmacokinetic–pharmacodynamic (PKPD) model. Through simulations, the model was applied to explore the clinical potential of such drug combination to overcome highly resistant bacteria.

Methods: The clinical isolate *Klebsiella pneumoniae* ARU613, an extended-spectrum β-lactamase and carbapenamase producing strain, resistant to both MIN and PMB, was selected for the study. Minimum inhibitory concentrations (MICs) for MIN and PMB were 12mg/L and 16mg/L, respectively. ARU613 was first exposed to a wide range of concentrations (0–64 xMIC) of either MIN or PMB alone with the number of colony forming units per mL (CFU/mL) counted at pre-determined time points between 0-28 hours. The generated data was used for the development of single drug PKPD models, which after their effects were combined, guided the selection of a limited number of informative drug combination TKS to be performed. Thereafter, the drug combination TKS data were used to update the PKPD model and interaction functions (the power interaction model [2], Bliss independence model [3] and general PD interaction (GPDI) model [4]) were explored. L2 [5] and M3 [6] methods were used to handle replicate CFU counts and below limit of detection data, respectively. Modelling was conducted in NONMEM 7.4.2. Visual predictive checks (VPC) implemented in PsN 4.7.15 were generated for model evaluation. Reported clinical population PK models for MIN [7] and PMB [8] were subsequently connected to the final PKPD model to predict the combination drug effect in simulated patients with an initial bacterial load of 6.8 log10 CFU/mL.

Results: Both MIN and PMB single drug models were based on the self-limiting bacterial growth model [9] in which bacteria transfer between 2 compartments residing 1) drug-susceptible, growing bacteria and 2) non-drug-susceptible, non-growing bacteria. The observed regrowth at later time points was here described by adaptive resistance models for both drugs. A model with a resistant subpopulation did not describe the data equally well. The observed TKS data indicated a benefit for combining MIN and PMB against ARU613. A synergistic effect of MIN and PMB was identified in the PKPD model where the GPDI interaction model described the data the best; PMB enhanced the MIN bacterial killing effect in a concentration-independent manner while the impact of MIN on PMB could be ignored. The estimated interaction parameter, which inclusion reduced OFV by 62 units ($P < 0.001$, $df = 1$), indicated that MIN potency for bacterial killing increased 53.5% in the presence of PMB. VPC plots demonstrated that the developed model could adequately describe the observed CFU counts. Predictions based on human PK indicated that clinically available high dosage regimens of MIN+PMB could keep bacterial counts below the start inoculum for more than 24 hours for the investigated strain resistant to the individual antibiotics.

Conclusions: We successfully developed a semi-mechanistic PKPD model describing MIN and PMB interaction on carbapenem-resistant *Klebsiella pneumoniae.* Model predictions where concentrations from

population PK models drove the bacterial killing supported clinical use of MIN and PMB in combination to overcome infections caused by highly resistant strains.

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I-76: *Meng Zhaoling* Real World Evidence and Model-informed Drug Development – an antidiabetic drug cardiovascular outcome case study

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Objectives: Cardiovascular (CV) safety outcome study is routinely required in diabetes drug approval. Recent empagliflozin approval for CV indication provides an additional risk reduction option for type II diabetes (T2DM) patients with high CV risks [1] and, at the same time, presents a potential confounding in the CV effect assessment for future studies. Some patients might already take empaglifozin at the study start and some patients might initiate it during the study. Concomitant administration of empaglifozin with the study drug increases the CV effect assessment uncertainty, especially when there is imbalanced empaglifozin addition between treatments during the study. A CV outcome study for glucagon-like peptide-1 receptor agonists (GLP-1ra) class drug presents such a case. Although historical GLP-1ra CV outcome studies (LEADER [2] and SUSTAIN 6 [3]) can provide good assumptions for GLP-1ra CV effect compared to standard of care (SOC), currently, there is no clinical study available to assess the CV effect of concomitant administration of SGLT-2i and GLP-1ra. We analyzed real world evidence data to estimate this effect. With estimated effects, necessary models of the study drug and planned study design, clinical trial simulations (CTS) were used to assess the impact of this confounding and the study probability of success (POS) for a GLP-1ra drug CV outcome study.

Methods: First, PopPK and PK/HbA1c exposure-response models were used to simulate patients' HbA1c over time for GLP-1ra and SOC arms based on the planned CV outcome study design. Secondly, literature and internal CV outcome studies were used to understand and model antidiabetic medication addition during the study, especially imbalanced addition between treatments due to differential HbA1c control. Then, a real world claim database, Truven, was used to estimate the CV effects of SGLT-2i addition, either concomitantly to GLP1-ra or alone. SGLT-2i class was assessed in the analysis considering AstraZeneca's CVD-REAL study [4] showing SGLT-2i, as a class, significantly reduced CV risks versus other T2DM medicines. Using the Truven database, T2DM patients started on 1st GLP-1ra were included in the analysis. Baseline characteristics matched T2DM patients never used GLP-1ra but started other new antidiabetic medication during the same time period were included as the SOC arm. Patients' age, gender and SGLT-2i baseline usage etc. were used in the matching. The estimated GLP-1ra vs. SOC and GLP-1ra + SGLT-2i vs. SGLT-2i effects were estimated and integrated in the CTS along with PK, PK/PD, concomitant medication addition models, and various design factors such as sample size, enrollment rate, event rates and study dropout rates. Based on the marketing prediction of empaglifozin patient utilization during the expected study period, different percentages of patients on empaglifozin at the study start and initiation during the study were simulated. The influential factor(s) for the study outcome were explored and identified.

Results: Imbalanced antidiabetic medication additions were consistently observed in historical GLP-1ra CV outcome studies, where ~20% and ~30% concomitant antidiabetic medication were observed for GLP-1ra and SOC arms, respectively. The imbalanced additions were hypothesized as due to lack of HbA1c control in SOC arm compared to GLP-1ra arm. An empirical concomitant antidiabetic medication addition model during the blinded study phase under differential HbA1c control of SOC and GLP-1ra arms was established using an internal historical CV outcome study. The real world evidence data estimated a GLP-1ra vs. SOC CV benefit ~10% reduction and smaller GLP-1ra+SGLT-2i vs. SGLT-2i CV benefit. 10% to 50% SGLT2-i patient

usage prevalence were assumed and tested in the CTS. The simulation indicated a small impact of differential SGLT-2i addition during the blinded study phase unless there was a fairly large % SGLT-2i patient usage. Therefore, the percentage of patients on SGLT-2i can be monitored during the study to mitigate the risk.

Conclusion: In this exercise, explicit and informative assumptions are essential in addition to appropriately established modeling framework to mimic a future CV study. Real world data was used to estimate the concomitant CV effects with/without empagliflozin and inform the CTS.

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I-77: *Yi Zheng* Effect of pregnancy on raltegravir free concentrations

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Objectives: Raltegravir can be used for the prevention of mother-to-child HIV transmission, especially when a rapid decline of HIV RNA load is necessary. Physiological changes during pregnancy have an impact on raltegravir elimination. Indeed, exposure of total raltegravir was shown to decrease from 29 to 50% during the third trimester of pregnancy compared to postpartum[(1)]. However albumin level is known to be lowered during pregnancy which could increase the active free fraction of the drug and reduce this effect. The objective of this study was to describe the unbound, total and glucuronide raltegravir pharmacokinetics during pregnancy.

Methods: The RalFe ANRS160 study was a non-randomized, open label, multicenter phase II trial in HIV-infected pregnant women receiving raltegravir 400 mg twice daily. Samples were collected during pregnancy (between 30 and 37 weeks of amenorrhea), at delivery and at postpartum (4 to 6 weeks after delivery). None of these women received an antiretroviral drug which could interact with raltegravir. Free raltegravir, total raltegravir and raltegravir glucuronide concentrations were measured using a validated liquid chromatography-tandem mass spectrometry and ultrafiltration methods. Aspartate transaminase, alanine transaminase, creatinine, biribuline and albumin of each sample were systematically measured. Furthermore, raltegravir has been shown to be primarily metabolized by the UDP-Glucuronosyltransferase (UGT1A1) and to be a substrate of the drug efflux transporter P-glycoprotein(PgP)[(2)]. Two polymorphisms, one in UGT1A1 and another in P-glycoprotein, were also genotyped by sequencing and real time PCR and respectively. A population pharmacokinetic model was developed by using NONMEM software.

Results: A total of 414 samples were collected from 43 women (aged from 23.3 to 45.9 years old) in which free, total and glucuronide raltegravir concentrations were measured. Free raltegravir was described by a one-compartment model with first order absorption and lag time, evolving either to bound raltegravir (by a linear binding to albumin), or to glucuronide raltegravir (through an additional compartment) or to a first order elimination. The influence of body weight, age, aspartate transaminase, alanine transaminase, creatinnie, biribuline and two polymorphisms were evaluated for the raltegravir pharmacokinetics analysis and no effect was found. Pregnancy increased free raltegravir clearances: by 26% for glucuronide formation which could be explained by increased activity of UGT1A1 during pregnancy and 17% for other elimination. During pregnancy, trough concentrations and exposures decreased by 28 and 37% respectively for total raltegravir and by 25 and 22% respectively for free raltegravir. The decrease was negligible for the glucuronide form.

Conclusions: This is the first data reporting free and glucuronide raltegravir pharmacokinetics during pregnancy. Pregnancy effect was moderate on the active raltegravir free fraction, especially when compared to its intersubject variability. Our data suggest that this pregnancy effect could be considered not to be of clinical importance, raltegravir does not need to be modified during pregnancy.

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I-78: *Xiao Zhu* Application of pharmacometrics to stimulus response models to describe signalling profiles of the cannabinoid-1 receptor

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Objectives:

Cannabinoid type 1 (CB_1) receptor is G-protein coupled receptor (GPCR) present at high levels throughout the CNS [1]. CB_1 is an attractive therapeutic target for numerous central nervous system diseases, including neurodegenerative disease, multiple sclerosis and pain. However, despite the enormous therapeutic potentials, clinical application of CB_1 ligands has been hampered owing to their adverse on-target effects. Recently, interests have risen in the ability of ligands to differentially regulate multiple signalling pathways when coupled to a single receptor, termed biased agonism [2]. One emerging therapeutic strategy is to improve the selectivity and safety of drugs through the development of ligands that are biased towards selected pathways. Therefore, it is crucial to have a comprehensive understanding of ligand-biased signalling at CB_1.

The time course of the stimulus response system often means the bioassay of the pathway of interest does not achieve equilibrium. This is compounded by receptor internalisation which under positive ligand activation occurs over the same time course as other pathway measurements. Currently these experiments are analysed by using single time-point choice to represent a snapshot of the process at a time where the investigator believes an equilibrium has occurred and then assesses each pathway separately. A full kinetic model is required in order to quantitatively assess the time-dependent modulation of the receptor by ligands and provide novel insights into the complex interplay among ligands, receptors and pathways.

The aims of current study was to develop a mechanism-based model that quantitatively describes the time course data from internalisation, phospho-ERK (pERK), and cyclic AMP (cAMP) pathways coupled to CB_1 receptor.

Methods:

Data

The internalisation was determined utilizing a live cell antibody feeding technique[3]. The terminal sampling was performed at 0, 2, 4, 8, 15, 30, and 60 min. Quantification of pERK was performed using the AlphaScreen SureFire kit (Perkin Elmer) [4]. The terminal sampling was performed at 1, 3, 4, 5, 6, 8, 12, 20, 40 and 60 min. cAMP was measured using a kinetic BRET assay (CAMYEL) [3]. Forskolin (FSK) was added to stimulate the synthesis of cAMP. The real time sampling was performed every 0.4-0.5 min for 20 min.
All the assays were performed under multiple concentration levels of six CB_1 ligands.

Model

The stimulus response model incorporated a transducer function (f, rectangular hyperbola in this study) to convert stimulus (S, resulting from receptor occupancy) into response, which allowed the response to represent a potential cascade of cellular or tissue signalling [5].

A mechanism-based stimulus response model was developed to describe the time course of three pathways sequentially using a PPP&D modelling framework:
1) Internalisation was described by a target-mediated drug disposition model with a quasi-steady state assumption [6].
2) pERK was described by an indirect response model [7]. The ligand effect was added via stimulus response model with stimulation on the synthesis rate.
3) cAMP was described by an indirect response model with capacity limited stimulation by FSK ([Emax*FSK]/[EC50+FSK]) on the synthesis rate of cAMP [7]. The ligand effect was added via a stimulus response model with inhibition on the synthesis rate.

Due to the intensive sampling in cAMP measurement, an AR(1) model was used to account for correlation in the residual errors[8].

The model was implemented in the ADVAN13 subroutine in NONMEM 7.3 [9]. The estimation method was FOCE-I.

Results:

The developed model adequately described the observed data. All model parameters were precisely estimated (<50% RSE) and within physiological ranges or agreed with values reported in the literature. The internalisation rate constant (from 0.028 to 1.05 min^{-1}) was generally much faster than the receptor degradation constant (0.0015min^{-1}, 15% RSE). For the pERK pathway, the estimated system maximal stimulation was 68.8 fold over baseline (11% RSE). The estimated duration of stimulation was 3.68min (2% RSE), which was consistent with observed peak time (from 3 to 5 min). For the cAMP pathway, the estimated system maximal inhibition was 0.718 fold over baseline (3% RSE).

Conclusions:

The joint model provided a reasonable description of the dynamic change of CB_1 receptor, leading to a better understanding of CB_1 system. In so doing, it could facilitate the discovery of novel therapeutics with improved selectivity and safety.

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II-01: *Esther Encinas* Population pharmacokinetic modelling of the antihistamine bilastine in children within the context of a model informed paediatric drug development approach

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Objectives: Bilastine is a non-sedating H1 receptor antagonist approved for treatment of allergic rhinoconjunctivitis (AR) and urticaria (U) in adults at the oral (p.o.) dose of 20 mg once daily (OD) [1]. Optimal attributes can be anticipated for its clinical use in paediatrics due to its favourable safety and tolerability [2] and age-independent PD profile [3]. The aim of this work was to characterize bilastine PK in children through population modelling of data from clinical trial BILA-3009/PED ("Multicenter, International, Adaptive, Open-label, Repeated Administration PK Study of bilastine (10 mg/day) in Children from 2 to <12 years with AR or U") as part of bilastine paediatric drug development. The primary objective was to ascertain whether the proposed dose in the above paediatric subset (10 mg/day) matches systemic exposure seen in adults at the 20 mg/day dose.

Methods: BILA-3009/PED was an adaptive limited sampling confirmatory study, optimized by means of an ontogenic predictive PK/PD model developed in children between 2 and 12 years based on prior knowledge [3]. The paediatric PK clinical dataset comprised a total of 31 patients from 4 to <12 years treated with 10 mg oral bilastine daily (sparse PK sampling performed up to 24 h following administration of the 6^{th} dose). PopPK models were developed in NONMEM, FOCE method. One and two compartment disposition models with first-order absorption and possible contribution of a lag time were explored. The influence of covariates (e.g. age, body weight, height, sex and creatinine clearance) was then evaluated by a stepwise procedure. Final model establishment and validation was done using standard statistical and diagnostic criteria for parametric non-linear mixed effects models, including goodness of fit plots, visual predictive check (VPC) and posterior predictive check (PPC). Suitability of the final paediatric dataset to fulfill the trial stopping criteria (i.e., model completeness and non-dependence of exposure on decreasing age) was also evaluated. In a final step, the popPK model along with observations and additional analyses were used to assess the suitability of the selected paediatric dose (10 mg/day) through comparison of PK metrics in children with those in adults (20 mg/day).

Results: A two-compartment disposition model (same structure as for bilastine PK in adults [4]) with a lag time and proportional residual error provided the best description of the paediatric observations. Parameter estimates were: Ka, 1.29 h^{-1}; CL/F, 12.5 L/h; Vc/F, 19.7 L; Vp/F, 17.4 L; Q/F, 2.01 L/h; Tlag, 0.183 h. The interindividual variability (modelled as exponential) was well defined and significant for Ka and CL/F. None of the studied covariates was significantly predictive for inclusion. Final popPK model was positively qualified and its predictive capacity was confirmed at all ages recruited hence supporting that the entire group of children [4 to <12 years] belongs to the same PK population (stopping rules pre-stablished to finalize the trial were thus fulfilled). Children from 2 years were deemed to belong to the same population as well, given that the physiology concerned is already mature by this age, as further supported by a number of additional analyses (including confirmation of ontogenic assumptions and physiological interpretation of bilastine PK processes) [3]. No significant difference was observed in AUC and C_{max} between paediatric age groups, all of which were well within the range observed in adults after the

therapeutic dose (20 mg daily). Min-Max range for $AUC_{0\text{-}24h}$ was 958-2110, 532-1653 and 481-2528 ng·h/mL in children <6 years, children ≥6 years and adults, respectively; corresponding values for C_{max} were 118-347, 129-447 and 83-924 ng/mL. The above approach supports the choice of 10 mg OD p.o. for the entire children subset, as further confirmed in a placebo-controlled safety trial including 509 children from 2 to <12 years (BILA-3312/PED) [5].

Conclusions: A popPK model characterizing bilastine PK behaviour in children aged from 4 to <12 years was successfully developed and positively qualified from observations in a limited sampling confirmatory study in paediatrics. The achievement of comparable (i.e., within the range) drug exposure to that observed in adults after the therapeutic dose of 20 mg, together with the additional integrative analysis, served to confirm the validity of the 10 mg daily dose for the target paediatric subset (2 to <12 years).

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II-02: *Aline Engbers* Pharmacokinetics of ibuprofen in very preterm infants with patent ductus arteriosus

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Introduction: The ductus arteriosus is a physiological shunt between the aortic arch and the pulmonary artery that closes spontaneously within hours after birth in term neonates. In preterm infants the ductus is often found to remain open, the so called patent ductus arteriosus (PDA) [1]. Because PDA with a significant left-to-right shunt is associated with increased morbidity and mortality, treatment of a hemodynamically significant PDA is commonly advised and achieved pharmacologically using ibuprofen [2]. However, discussion is still ongoing concerning the optimal dosage, duration and route of administration. An intravenous 3 day-course with 10 mg/kg on day 1 followed by 5 mg/kg on day 2 and 3 is currently suggested by the label, but regimens with either higher daily doses, continuous administration, and oral administration are suggested to be more effective [3]–[5]. To date there is limited information on target concentration or exposure that needs to be achieved, or specific pharmacokinetic information that may guide the use of ibuprofen across this population.

Objectives: The objective of this study was to develop a population PK model for ibuprofen in preterm infants for the treatment of PDA.

Methods: In a prospective cohort study designed to examine the PK and PD of off-label used drugs in preterm infants, neonates born with a gestational age between 24 and 32 weeks in four Dutch neonatal intensive care units were considered for inclusion. Eighty neonates receiving ibuprofen treatment for PDA closure were evaluated. For 73 of these patients detailed information regarding intravenous ibuprofen dosing and patient characteristics were available at the time of data analysis, providing 218 plasma samples in which either R-ibuprofen, S-ibuprofen or both could be quantified using a validated UPLC-UV (ultra-performance liquid chromatography-ultraviolet) analysis method. The median gestational age (GA) of this study population was 26.1 (range 24.0 – 30.1) weeks, and median postnatal age (PNA) was 6 (range 1 - 32) days. The median cumulative dose of ibuprofen was 25 (range 7 to 98) mg/kg and the duration of therapy was median 2 days (range 1 to 14 days).

The total concentration of ibuprofen (sum of R- and S-ibuprofen) plasma concentrations was modelled using NONMEM V7.3.0 [6]. GA, PNA, postmenstrual age, gender, birthweight and actual bodyweight (WT) were tested as covariates. Covariates were included based on a forward inclusion and backward exclusion principle ($p<0.05$ and $p<0.01$ respectively), and were only included if their effect was biologically plausible. The final model was validated using normalized prediction distribution errors and by performing a bootstrap.

Results: In a one-compartment model, population mean clearance (CL) was estimated 0.011 L/h with an interindividual variability (IIV) of 64.3%, (RSE 8%), and the mean central volume of distribution (Vd) 0.325 L (13.4% IIV, RSE 6%). IIV in CL was best predicted by the covariates PNA and GA ($p<0.0001$ and $p<0.001$ respectively). CL linearly increased by 23.7% per week of gestation. For PNA a power function with an estimated exponent of 1.81 (RSE 11.5%) led to the best fit. WT was found to influence Vd, which was best

described by a power model with an exponent of 0.511 (RSE 29%). All parameter estimates were within the 95% confidence intervals as calculated by the bootstrap.

Conclusions: Ibuprofen CL in preterm infants is affected by both GA and PNA. This underlines the need for age specific ibuprofen dosing guidelines. The results of this analysis can be used as a basis for exploring the stereopharmacokinetics of the R- and S-enantiomers of ibuprofen, ultimately to guide individualised treatment of preterm infants with ibuprofen.

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II-03: *Elvira Erhardt* Bayesian knowledge integration for an in vitro–in vivo correlation (IVIVC) model

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Objectives:

In vitro–in vivo correlation (IVIVC) methods play a key role in the drug development and optimization of formulations. An IVIVC is defined by the Food and Drug Administration as the mathematical relationship between the in vitro characteristics of a dosage form and its in vivo response. This tool can act as a surrogate for bioequivalence or bioavailability testing in human subjects, thus support biowaivers and thereby reduce cost and duration of the optimization process [1]. However, most of the current IVIVC models entail complex and potentially unstable mathematical deconvolution operations and are assessed applying purely frequentist methods, such as linear regression, on averaged data [2]. We suggest a new predictive model for the pharmacokinetic (PK) data of a controlled release (CR) formulation through combination of an in vitro model of the drug release with an in vivo immediate release (IR) model. Simultaneously, we account for the uncertainty in the parameter estimates.

Methods:

The proposed 3-step IVIVC approach includes (a) a frequentist nonlinear mixed effects model [3] for the in vitro release data; (b) a frequentist population PK compartment model for the in vivo IR data (fitted using the NLMIXR package [4] in R); and (c) a system of ordinal differential equations containing the submodels (a) and (b), which approximates and predicts the in vivo blood concentration-time, using in vivo controlled release data. The innovation consists of splitting the parameter space between submodels (a) and (b) versus (c) and, subsequently, accounting for the uncertainty around these parameters via a Bayesian framework (in the software STAN [5]). That is, estimates from the first two frequentist submodels serve as priors for the Bayesian hierarchical third submodel; the prior standard deviations account for the variability around the previously estimated parameters [6]. We demonstrate the application of the method using the study data of a transdermal patch, in (a) and (c), and of an intravenous infusion, in (b), as an example.

Results:

The in vitro release was well-approximated by a Weibull input-function; a three-compartment model described the IR concentration data of the population PK adequately. The combined ODE converged with a reasonable run-time and the predicted drug concentration-time profiles are comparable with the in vivo observations. Thus, the developed IVIVC model led to a satisfactory estimation of the case study.

Conclusions:

The Bayesian method explained ensures a natural integration of knowledge from one source of information into the other, from in vitro to in vivo, making the best use out of our prior information and proper modelling of uncertainty. Many authors before us used plug-in estimates from the first stage of PK modelling without accounting for their uncertainty; we believe this may introduce an undue over-confidence in the model. Our generally applicable two-stage Bayesian approach is combining the benefits

of one- and two-stage frequentist models. Therefore, it is an improvement of the current IVIVC methodology, where techniques based on averaged data and complex and potentially unstable mathematical deconvolution [7,8] are the standard.

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II-04: *Ruben Faelens* Benefits of TDM in clinical management: a test case in infliximab for ulcerative colitis

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Introduction Infliximab (IFX) is used in patients with ulcerative colitis (UC) to achieve mucosal healing (MH, defined as Mayo endoscopic sub-score <= 1). A pharmacokinetic/pharmacodynamic (PKPD) model was established [1] linking IFX exposure to probability of mucosal healing (pMH), based on a previously published dataset [2]. The model allows to optimize dosing to increase population exposures, which is predicted to improve clinical outcomes. Compared to open loop dosing, therapeutic drug monitoring (TDM) may be used to optimize dosing even further.

Objective To evaluate different dosing regimens towards obtaining mucosal healing, and the potential benefit of TDM-based dose adjustment.

Methods For simulation, the base model without covariates on PK was used: a 1cpt model with between-subject variability (BSV) and within-subject variability (WSV) on Ke (CVs%=39; 21.5) and V (CVs%=42; 14.5). The PD model predicts pMH based on individual cumulative area under the curve (CAUC) at day 84 and baseline score. For targeted dosing, a pMH of 70%, predicted to correspond to a CAUC of 3400µg/mLday or 4800µg/mLday for a baseline score of 2 or 3 respectively was aimed for.

The following dosing regimen were evaluated (dosing at weeks 0, 2 and 6):

1. 3x5mg/kg as per the label.
2. 3x10mg/kg.
3. Fixed dose based on baseline score (open loop). 3x600mg and 3x800mg is predicted to achieve pMH=70% for a baseline of 2 and 3 respectively.
4. As (3), with further adjustment at day 14 using Bayesian estimation of BSV based on serum concentration (closed loop), and selecting the dose that is predicted to reach individual pMH of 70%.
5. As (4), assuming perfect knowledge of BSV.

To evaluate probability of study success (PoSS), a chi-squared test on the number of patients achieving MH was used to compare both arms. Simulations were implemented using Simulo Expert v7.2. TDM was implemented using the TDMore framework, available at https://github.com/rfaelens/tdmore .

Results Reported values are mean (for dose or pMH) or median (for CAUC) values [90% prediction interval]

Scenario	Average Dose (mg)	CAUC (µg/mL*day) for baseline score of 2 (target=3400)	CAUC (µg/mL*day) for baseline score of 3 (target=4800)	pMH (%)

(1) 5mg/kg	360	2162 [811,5521]	same	54 [27,77]
(2) 10mg/kg	720	4314 [1626,11077]	same	70 [46,87]
(3) Open loop	701	3676 [1457,8920]	4878 [1932,11899]	70 [48,86]
(4) Closed loop	697	3527 [2519,5235]	4941 [3534,7277]	71 [63,78]
(5) Perfect knowledge of BSV	701	3425 [2638,4483]	4837 [3718,6305]	70 [64,76]

Scenario	**Arm 1**	**Arm 2**	**Patients per arm**	**PoSS**
Dose-controlled trial	5mg/kg	10mg/kg	100	57%
			167	80%
Exposure-controlled trial	pMH = 54%	pMH = 70%	100	60%
			156	80%

Discussion The pMH with the current regimen is 54% and confirmed in our simulations. Increasing the dose to 3x10mg/kg is predicted to achieve pMH of 70%. Dichotomisation of fixed dose by baseline Mayo score does not reduce the distribution of individual pMH, due to high BSV.

Closed loop dosing is predicted to reduce BSV of pMH. Note that this beneficial effect is not detectable on a population level, since the fraction cured in the population remains unchanged compared to a fixed dose regimen yielding identical average exposure. Any dose saved in over-exposed patients is equally consumed in under-exposed patients, resulting in identical average consumption of drug on a population level.

As N=167 patients per arm are needed to achieve a PoSS (power) of 80% at alpha=0.05, studies evaluating a 10mg/kg dose vs a 5 mg/kg dose should be adequately powered. An exposure-controlled trial does not greatly improve PoSS when evaluating efficacy of 5mg/kg vs 10mg/kg.

Conclusion Assuming PK drives PD, higher induction doses than 5mg/kg should be explored, as they are predicted to have better outcomes. Compared to 5mg/kg, 10mg/kg is predicted to raise average exposure from 2150 µg/mLday to 4300 µg/mLday, and pMH from 54% to 70%. TDM aiming for a target exposure increases pMH for under-exposed patients, but decreases the pMH for over-exposed patients. Population pMH is therefore predicted to not improve using this technique, although individual probabilities of MH are equalized. Finally, an exposure-controlled trial is not expected to improve the power of studies using the MH dichotomous endpoint.

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II-05: *Dzhem Farandzha* Tacrolimus Population Pharmacokinetic Analysis with Pmetrics in Infants after Liver Transplantation – preliminary data.

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Objectives: Immunosuppression after liver-transplantation is of key importance for the survival of both the patient and the transplant. Tacrolimus has become the preferred immunosuppressant in liver transplant recipients due to its superior role in improving patient and graft survival in addition to the lower number of acute and steroid-resistant rejections as compared with cyclosporine [1]. Although its extensive inter- and intra-individual pharmacokinetic variability as well as the changing dose requirements with time are well documented, the literature on the distribution patterns of tacrolimus concentrations in liver-transplant infants is still quite scarce for obvious reasons [2]. The primary concern of this research was to conduct a pilot population pharmacokinetic study with tacrolimus in liver-transplant infants in the early post-transplantation period that could later be further developed with data from new patients.

Methods: The study involved 5 infants, median age 8 months (ranging from 2 months to 11 months), who underwent orthotopic liver transplantations between November 2010 and April 2015 at Lozenetz Hospital, Sofia. All patients received oral tacrolimus (Prograf®) twice daily at 8 am and 8 pm respectively in the intensive care unit (ICU) during the early post-transplantation period (ICU stay ranging from 30.5 to 44.5 days, median 41 days). Therapeutic drug monitoring (TDM) by trough level measurement was used to tailor the doses to fit in the therapeutic range. A total of 65 trough tacrolimus whole-blood concentrations were analyzed using Origin 9.0 and a p-value of ≤ 0.05 was considered as statistically significant. The pharmacokinetic (PK) population modeling was performed using Pmetrics [3]. The concentrations/time kinetics was best described by a one-compartmental absorption model with first order elimination. The absorption profile of tacrolimus was shaped by the first order absorption rate constant, Ka, lag-time (Tlag) and bioavailability (Fa) terms.

Results: The statistical distribution pattern of trough tacrolimus concentrations at the end of each dosing interval was characterized by non-Gaussian distribution pattern skewed to the right. The Q-Q plot confirmed the non-normal distribution pattern and revealed subgroups of trough tacrolimus concentrations deviating from linearity. The estimates of tacrolimus pharmacokinetic model parameters were presented as medians. Median absorption rate (Ka) and elimination rate (Ke) constants were 8.46 h^{-1} and 0.04 h^{-1} respectively. Volume of distribution (VD) was 0.09 L/kg. Lag time (Tlag) was 0.41 h. Bioavailability (Fa) was 0.38. Due to the small number of patients external validation on Pmetrics could not be performed. Internal validation was performed using the normalized prediction distribution errors (NPDE) method of Mentré and Escolano instead [4]. Plotting observed versus individual predicted tacrolimus concentrations yielded a correlation coefficient (r) of 0.81 with a p-value of <0.001.

Conclusion: The search through the current available literature did not yield results that could be compared to the findings presented here. More data from similar patients will enable us to perform external validation in addition to the analyses presented here, which will significantly improve the reliability of the predicted tacrolimus concentrations. The inclusion of additional covariates such as hematocrit, steroid dose and time after transplantation to the model could also potentially improve the predictions. Pharmacometric tools such as Pmetrics could then successfully be used to build pharmacokinetic models for specific groups of patients that could later be implemented in computer-based dose individualization strategies.

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II-06: *Felix Held* Bayesian hierarchical model of oscillatory cortisol response during drug intervention

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Introduction: Oscillating biomarker response-time courses challenge modelling of drug intervention. A periodically recurring pattern is typically seen for the stress hormone cortisol. This pattern can be captured by mechanism-based turnover models. However, analysing experimental data requires new mathematical techniques. Bayesian hierarchical modelling allows for full quantification of parameter uncertainty while also capturing the population aspects typical to nonlinear mixed effects modelling. Inter-occasion variability (IOV) is incorporated in addition to inter-individual variability (IIV).

Objectives:
- Propose a model based workflow for oscillating baseline turnover models including IIV and IOV.
- Apply the workflow to cortisol- and dexamethasone time-series data obtained from horses.
- An additional aim was to predict test performance of a two-sample dexamethasone suppression test-protocol (DST-protocol) [1, 2] in horses.

Methods: Cortisol- and dexamethasone time courses were collected [1]. Four different doses of dexamethasone were given (no drug and 0.1, 1, 10 µg/kg bolus + 0.07, 0.7, 7 µg/kg infusion over three hours). The pharmacokinetic/pharmacodynamic model was adapted from [1]. Cortisol was described by a turnover model with oscillating turnover rate (average baseline k_{avg}, amplitude α, phase-shift t_0) and fractional turnover rate k_{out}. Drug intervention was modelled with Hill-type suppression (maximum inhibition I_{max}, potency IC50, hill coefficient n). Dexamethasone exposure was described by a two-compartment model. The model was then extended to a population model by introduction of inter-individual and inter-occasion effects. The final model was inferred from data using a Bayesian framework with the Hamiltonian Monte Carlo algorithm in Stan [3]. Ordinary differential equations were solved analytically for the case of constant drug exposure. The performance of the two-sample DST-protocol was studied by calculation of the probability that cortisol is suppressed below a prescribed threshold (denoted *success probability*). These probabilities were predicted by model simulations at different dose levels of dexamethasone.

Results: The proposed model described the data well. Pharmacodynamic population parameters were estimated with median (95% credible intervals): k_{avg} = 12.91 (9.98, 16.67) µg L^{-1} h^{-1}, α = 5.91 (4.02, 8.61) µg L^{-1} h^{-1}, t_0 = -4.10 (-5.95, -2.07) h, k_{out} = 0.32 (0.27, 0.40) h^{-1}, I_{max} = 0.97 (0.92, 1.0), IC50 = 0.0329 (0.0166, 0.0703) µg L^{-1}, n = 0.95 (0.73, 1.24). Low precision was found in the standard deviations of the random effect parameters. IIV and IOV present in the data were captured by the model. The average cortisol response level and its amplitude are suppressed with respect to magnitude and variability with increasing exposure to dexamethasone. The maximum and minimum levels of cortisol response were also suppressed by increasing exposure to dexamethasone. Mathematical expressions were derived describing cortisol oscillations with inhibition and were consistent with experimental data. The DST-protocol is challenged for intravenous injections below 20 µg/kg. The probability of success with the DST increases with increasing

doses greater than 30 µg/kg. The oscillatory behaviour of cortisol response and the different levels of variability (IIV and IOV) will greatly challenge the applicability of the outcome of the present DST-design.

Conclusions:
- New techniques were developed for graphical analysis of the oscillatory cortisol response
- These were successfully applied to equine cortisol data after dexamethasone intervention
- Oscillatory behaviour and level of variability had great impact on the sparse-sample DST-design

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II-07: *Kevin Feng* Selecting in vitro dissolution tests using population pharmacokinetic modelling to help bioequivalence studies

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Objectives: Before conducting bioequivalence (BE) studies or any related pilot studies for in vivo clinical trials, selecting an appropriate in vitro dissolution test is a key analytical test for detecting physical changes in an active pharmaceutical ingredient (API) for any solid oral dosage forms. The main objective of this work is to build population pharmacokinetic (Pop-PK) models with direct in vitro-in vivo correlation (IVIVC) for selecting effective test technology matching the in vivo human absorption of API from the innovator and hence to indicate the performance of the test formulation (T) – either success or likely failure mechanisms related to the in vivo human studies.

Methods: Nifedipine was taken as an example to demonstrate the benefit of Pop-PK modelling with direct IVIVC. A total of 34 in vitro dissolution experiments were performed using USP1, USP2, USP3, and USP4 methodologies with various combinations of pH, volumes (mL), media type (FaSSGF with or without grapefruit juice), rotation speed (rmp), dipping rate(dpm), flow rate (mL/min), and ethanol content (%v/v) [2]. The in vitro dissolution profiles were then fitted by using the best selected sigmoidal models such as a Hill equation or cumulative Weibull distribution. The fitted in vitro dissolution models were then differentiated to provide the input rate added to the IVIVC models which were directly incorporated in PK models [3]. Nonlinear mixed effect modeling (NLME) was used to estimate PK models with direct IVIVC by fitting 30 subjects blood samples created from [4, 5,6] for both Caucasian population and south Asian population. The best fitted models with related in vitro dissolution experiments were selected for test formulation dissolution experiments. Both test and reference formulation (T&R) in vitro dissolution were used for simulation using parallel design and 2 by 2 crossover design. Simulated PK parameters such as Cmax and AUC were used to determine the bioequivalence between T&R using ANOVA analysis.

Results: Both Caucasian and south Asian data show consistent results for the in vitro dissolution test methods that USP2 is the preferred method and in vitro dissolution tests without grapefruit juice match better with the in vivo concentration. Lower bound and upper bound dissolution profiles for T are created to test the BE with R. The BE test results showed that the T is bioequivalent with the R if the variation of in vitro dissolution of the T is within the test bounds. The results indicated that the T is more likely to be successful if the in vitro dissolution is within the test bounds and only if the in vitro dissolution experiments were done using the selected test technology.

Conclusions: The direct IVIVC method using population PK analysis is a novel approach for bioequivalence studies. The method helps to identify in vitro dissolution tests and test bounds, to propose ranges of dissolution profiles and hence to increase the successful rate of test formulation and hence reduce the number of BE studies performed during the initial approval process or certain scale-up and post approval changes [1].

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II-08: *Yan Feng* A Mixture Tumor Growth Dynamic (TGD) Model to Describe Differential Patterns of Longitudinal Tumor Response of Advanced Melanoma Patients Treated with Ipilimumab

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Introduction: Ipilimumab (IPI) was the first immune-checkpoint inhibitor (ICE) to demonstrate an improvement in overall survival (OS) of advanced melanoma (AdvMel) patients [1], and the approved dosing regimen for AdvMel in the US and EU is 4 doses of 3 mg/kg, given once every 3-weeks (Q3W). The benefit-risk of 10 mg/kg vs 3 mg/kg IPI in AdvMel was evaluated in a post-approval randomized phase 3 study (CA184169) [2], as objective tumor response was higher with 10 mg/kg in a phase 2 dose-ranging study [3]. The overall survival (OS) of AdvMel patients in CA184169 treated with IPI 10 mg/kg Q3W (4 doses) was significantly better than that of the 3 mg/kg dose. However, the objective response rate (ORR) by RECIST criteria, duration of response, and progression free survival (PFS) were similar in both dose arms. Characterization of the tumor burden (TB) time-profile may enable identification of one or more features of tumor response that are associated with OS following treatment with ICE agents.

Objectives:

- Characterize the TB time-profile of patients treated with ipilimumab treatment, by a model-based description of longitudinal tumor burden data
- Utilize the model to assess differences in patterns of TB time-profiles

Methods: The TB time-profiles of AdvMel patients in CA184169 who received ipilimumab, and for whom tumor burden data were available (N=345 for 3 mg/kg; N=344 for 10 mg/kg) were described by a nonlinear mixed-effects TGD model. The sum of the longest diameters of target lesions was used as a surrogate for TB. The TB at a given time (t) =baseline tumor burden, first-order shrinkage rate, linear growth rate, and the tumor burden at steady-state, respectively. A unimodal model and mixture models with 2 or 3 subpopulations were evaluated. TBSS was only defined for mixture models with a no growth subpopulation (TG fixed to 0). Bayesian information criterion (BIC) was used to guide model selection.

Results: The TGD model with 3 subpopulations provided an adequate description of the observed data, and had the lowest BIC value among tested unimodal and mixture models. The 3 (no growth, intermediate, and fast tumor growth) subpopulations determined by the mixture model identified subjects with qualitatively different tumor growth dynamics, as evidenced by differences in the distributions of TG and TS values. TB0 was higher in subjects in fast tumor growth subpopulation than the other two subpopulations. The TS was similar in both dose arms, but the TG of patients in the 10 mg/kg arm was ~30% slower than that of patients in the 3mg/kg arm (0.020 vs. 0.029 cm/week). The fractions of patients in the 3 and 10 mg/kg dose arms who were categorized into the no-growth subpopulation (representing durable response) were approximately 15.1% and 21.7%, respectively.

Conclusions: The TGD profiles of AdvMel patients treated with IPI were adequately described by a mixture TGD model, with 3-subpopulations (fast, intermediate, and no-growth). Even though PFSwas similar between 3 and 10 mg/kg, the proportion of subjects achieving durable responses were higher, and tumor progression rate was lower in patients who received 10 mg/kg relative to those received 3 mg/kg.

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II-09: *Carlos Fernandez-Teruel* Drug exposure / response model for neutropenia with lurbinectedin in cancer patients

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Objectives: Lurbinectedin is a new anticancer agent that inhibits activated transcription, induces DNA double-strand breaks generating apoptosis and modulates tumor microenvironment. Reversible myelosuppression (anemia, lymphopenia, leukopenia, neutropenia and thrombocytopenia) is the most frequent abnormality related to treatment with lurbinectedin. In this work, data from two phase I and three phase II trials were pooled to evaluate the time course of absolute neutrophil count in patients treated with lurbinectedin as single agent.

Methods: The dataset contained 2069 absolute neutrophil count observations from 156 patients, with lurbinectedin doses ranging from 0.02 to 6.9 mg/m^2, given as 1-h i.v. infusion and at schedules of Day 1, and Days 1 and 8 in cycles of three weeks. The absolute neutrophil count dataset was merged with the pharmacokinetic dataset, with 2673 lurbinectedin plasma concentrations available from cycles 1 and 2 for those patients. The population PK/PD model for neutropenia was developed based on lurbinectedin pharmacokinetic model, which was linked to a transit model based on the proposed by Quartino [1]. Once the base model was achieved, several covariates where explored to identify the sources of variability. Datasets were produced with SAS Enterprise Guide v7.11, models were executed with NONMEM 7.3 and covariate analysis was performed by using stepwise covariate model from PsN v4.6.0. Additionally, the final model was validated through pcVPC and bootstrap analysis also from PsN.

Results: A neutropenia model with transit compartments and feedback effects on mean transit time and proliferating cell pool was suitable to describe the time-course of absolute neutrophil count. The absolute neutrophil count dataset was Box-Cox transformed with lambda of 0.2465 which was the optimum value for the current dataset, while the pharmacokinetic dataset was log-transformed. Both residual variabilities were managed as additive errors with inter-subject variability. The observed baseline of absolute neutrophil count was used as covariate acknowledging the neutrophils residual variability following the B2 procedure [2]. The following covariates modified the neutropenia incidence: absolute neutrophil count at baseline, alpha-1-acid glycoprotein, presence of ascites, the use of Granulocyte-colony stimulating factors (G-CSF), prior use of anthracyclines, and the use of CYP3A inducers. The lurbinectedin drug effect was included into the model using a sigmoid Emax function governed by the parameters Emax, EC50 and a Hill exponent with a value of 2.16. The use of G-CSF doubled EC50 and almost cut in half the mean transit time which markedly reduced neutropenia.

Conclusions: This modeling exercise has characterized the relationship between lurbinectedin exposure and neutropenia incidence, identifying the sources of variability. The model shows that lurbinectedin-induced neutropenia can be managed with dose reductions and/or G-CSF, and is useful for supporting the design of new clinical trials.

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II-10: *Martin Fink* Informative study designs: The value of within-subject dose-escalation in the 'Espresso design'

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Objectives: Drug development aims for most informative experimental designs while minimizing exposure of animals and patients to invasive procedures and potentially harmful drugs. Dose-concentration-response information can be generated efficiently by investigating a range of exposures within individuals rather than relying on between subject analyses, either by following individuals' responses as their drug concentrations decline or by applying within-individual dose escalation. Here, we evaluate the robustness of a within-individual dose escalation design ("Espresso design") in a non-human primate study to inform the first-in-human dose for monoclonal antibodies.

Methods: Optimal design software PopED [1] was used to evaluate 3 different study designs with 4 animals each: (a) "Standard design": all administered a high dose, (b) "Dose-spread design": spanning a dose range with 1 animal per dose, (c) "Espresso design": within-individual dose escalation with increasing dose-amounts every other day [2] (a similar approach has been published for an oncology Ph2-trial [3]).

A 1-compartment (cmt) taarget mediated drug disposition (TMDD) and a 2-cmt TMDD model with a mathematical approximation for immediate binding to a soluble target were investigated. The parameters were set to typical values for monoclonal antibodies. To assess the robustness of the study designs against the unknown binding coefficient in-vivo the Kd parameter was modified up and down 30-fold (thus a 900-fold range) and the relative standard errors (RSE) were derived with PopED. In the Espresso design, the time interval between up-titrations was also varied. When considering the appearance of anti-drug-antibodies (ADAs) after 10 days in all animals the data after their appearance was set to missing (as being unreliable) thus all sampling time points after day 10 were ignored.

Results: For the 1-cmt TMDD model, the Espresso design with exponentially increasing dose-levels up-titrated every other day provided only minor improvement over the other designs for the clearance of the drug, but was substantially better for estimating the clearance of the target (50% RSE versus more than 100% RSE for most Kd values investigated). Estimation of Kd and its inter-individual variability was limited by an additive error operating predominantly on the lower concentrations but proved also to be at least 2-fold better for the Espresso design. Of note, the Dose-spread design also out-performed the Standard design.

The superiority of the Espresso-design was more pronounced with the 2-cmt TMDD model. The standard design performed very poorly (only clearance of the drug was estimated with less than 100% RSE). The Dose-spread design gave good precision of parameters, except for the inter-individual variability of Kd. The Espresso-design out-performed the two other designs again with overall robust estimates of most parameters (<100% RSE). When including the 2nd compartment the up-titration interval of 2 days was slightly less optimal than an interval of 4 days.

When anti-drug-antibodies appear at Day 10 then none of the clearance parameters for drug and target were identifiable with precision in any of the designs. The remaining parameters were however estimated

with good precision with the Espresso design, as well as the Dose-spread design, but not the Standard design with only a high-dose.

Conclusions: The Espresso design with within-subject dose escalation proved more robust and efficient than Standard designs. It also allowed high exposure levels to be achieved in all subjects (for safety investigations) compared with a design which spread subjects across dose-levels. It provided good estimates of all parameters (except for clearances) in the first 10 days (e.g., in case of appearance of anti-drug-antibodies) and thus allowed for assessment of possible time-dependent changes of the underlying physiological system. In future practice, a mix of different design types will be applied to assess also additional study objectives, such as, for example, injection site reactions with high doses at the first injection.

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II-11: *Chiara Fornari* Development of a haematopoiesis systems pharmacology model for prediction of carboplatin induced bone marrow toxicity

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Introduction: Balancing anti-tumour efficacy with safety is an ongoing challenge in oncology. Drug-induced myelosuppression is a common dose limiting toxicity of cancer treatments, for both cytotoxic drugs, targeted therapies, and combinations [1]. Mathematical modelling has proven to be a powerful aid in understanding the mechanisms of drug-induced haematotoxicity, scaling results from animal models to humans, and designing optimized treatment regimens [2]. However, major limitations with existing approaches are that (i) due to the invasiveness of bone marrow (BM) biopsy, myelosuppression is inferred from blood counts, especially in humans, extrapolating to the unseen effects in the BM and, (ii) often, each blood cell type (e.g. neutrophils, platelets) is modelled independently[3]. In order to close these gaps and understand the heterogeneity observed in clinical outcome, this routine data obtained from blood must be supplemented with additional information, such the one from *in vivo* haematopoiesis systems [4]. Then, systems models help to understand differences in time-course and to characterize the underlying biology, that may otherwise be overlooked and, ultimately, they can aid translation from the pre-clinical studies to human.

Objectives: To develop a novel mechanistic model of carboplatin-induced myelotoxicity that can capture the overall myelosuppression profile in rat, i.e. from progenitor cells in the BM to different types of cells in the blood (neutrophils, monocytes, platelets, reticulocytes, and red blood cells).

Methods: Carboplatin-induced myelotoxicity was derived using *in vivo* rat data following different exposures to carboplatin (30mg/Kg on day 1; 40mg/Kg every 14 days for multiple cycles). More precisely, we analysed time-courses of neutrophil, monocyte, platelet, reticulocyte and red blood cell counts together with BM cellularity profiles (multi potent progenitor, common myeloid progenitor, and megakaryocyte-erythrocyte progenitor counts). The model is a system of ordinary differential equations, implemented in Matlab, using the Simbiology platform. The same platform was also used to perform model fits to data and simulations.

Results: A new systems pharmacology model was developed to capture the *essential* features of haematopoiesis, such as the role of stem cells, the process of differentiation into multiple lineages, and the interaction among different feedback mechanisms, [5]. Moreover, we modelled haematopoiesis as a whole system, where all lineages come from a common set of progenitors. Then, we fit this model to data from *in vivo* haematopoiesis systems, capturing the dose and regimen dependent Carboplatin-induced myelosuppression profile in rats. The model described how variations in the BM are mechanistically linked to those in the blood, and how the interaction among inputs from different lineages modulate progenitor proliferation and differentiation, giving rise to the observed changes in BM cellularity and blood cell counts.

Conclusion: Drug-induced myelosuppression remains a significant issue in oncology. We reviewed existing mathematical approaches for studying haematopoiesis and bone marrow toxicity, identified gaps in current understanding, and made future recommendations to advance further this vital field of safety research. In

particular, a major issue is obtaining observations from the BM, especially in humans, due to the invasiveness of BM biopsy. When this upstream information is not available, modellers generate hypotheses about the unseen drug effects, based only on drug concentration and blood counts. We developed a novel systems pharmacology approach based on *in vivo* rat data to link carboplatin-induced toxicity in the BM with effects in the blood, thus following the overall myelosuppression dynamics from progenitors to mature cells. The benefits of a model such as this include (i) improved physiological understanding of drugs effects, (ii) less inference of upstream outcomes from blood cell counts, and (iii) better characterization of the correlations existing among different types (and grades) of haematotoxicity. Lastly, this work represents a first step to establish animal model to build confidence in first time dose in man for translation. Therefore, by developing this further, we will learn more about the impact of therapeutics on the myeloid system and, potentially, develop a tool to translate pre-clinical results and guide treatment scheduling in the clinic.

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II-12: *Jose Francis* AADAC gene polymorphism and HIV infection affect the exposure of Rifapentine: a population pharmacokinetics analysis

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Objectives: Rifamycins play a key role in the multidrug treatment of tuberculosis. With its long half-life and excellent sterilizing activity, rifapentine is an attractive alternative to rifampicin and is increasingly used to treat active tuberculosis and latent infection. Like rifampicin, rifapentine demonstrates marked interpatient pharmacokinetic variability and its primary metabolic pathway involves deacetylation to 25-desacetyl rifapentine, which is mediated by human arylacetamide deacetylase (*AADAC*). The absorption of rifapentine is markedly increased by concomitant food administration. Like other rifamycin's, rifapentine is also known to cause autoinduction of its own metabolism. The success of anti-tuberculosis treatment is related to rifapentine concentrations, therefore single nucleotide polymorphisms substantially influencing its concentrations may be of therapeutic importance. The exposure of rifamycin's in humans is modulated by pregnane X receptor (*PXR*), constitutive androstane receptor (*CAR*) and solute carrier organic anion transporter (*SLCO1B1*) genes. The aim of this study was to determine the effect of functionally significant polymorphisms of *SLCO1B1*, *PXR*, *CAR*, and *AADAC* on rifapentine exposure.

Methods: The study included patients diagnosed with pulmonary tuberculosis from two clinical studies (RIFAQUIN and a two-stage activity-safety study of daily rifapentine referred to as "Daily RPE") [1,2]. In RIFAQUIN, rifapentine was administered in the continuation phase of anti-tuberculosis treatment either as 1200 mg once weekly or 900 mg twice weekly. In Daily RPE 450 or 600 mg were given daily during the intensive phase of treatment. For RIFAQUIN, pharmacokinetic assessment involved a rich (with a pre-dose and samples at 1, 2, 3, 5, 7, 10, 12, 26, and 50 h after dosing) or sparse sampling (samples drawn around 2, 5, and 24 or 48 h after dosing). The pharmacokinetic sampling for Daily RPE was done at approximately one month after starting therapy and samples were obtained either with a rich sampling schedule (with a pre-dose and samples at 0.75, 1.5, 3.5, 5, 12, and 24 h after dose), or sparse sampling (0.5-2 h and 5-8 h after dose). The plasma rifapentine concentrations were determined with a validated LC-MS/MS assay using rifaximin as internal standard. The lower limit of quantification (LLOQ) was 0.156 mg/L. Pharmacogenetic information was obtained by genotyping in a subset of patients from these studies. The pharmacokinetic data was analysed using NONMEM 7.4 with FOCE-I. The influence of gene polymorphism on rifapentine pharmacokinetics for patients with unknown genotype was identified using mixture modelling [3].

Results: A total 1144 drug concentration measurements were available for the final analysis, collected from 326 patients who are southern Africans with a median body weight and age of 56 kg and 32 years respectively. Pharmacogenetic information was available for 162 patients. The few observations below the LLOQ (n=7) were omitted from the analysis. A one compartment model with first order elimination and transit compartment absorption described the data well [4]. Allometric scaling with fat free mass for clearance and total body weight for volume of distribution were found to be best size predictors. In a typical patient, the values of CL and Vd were 1.33 L/h and 25 litres respectively. Patients who were homozygous for *AADAC* rs1803155 AA mutation were found to have 10.4% lower clearance. Patients who were infected with HIV had 21.9% lower bioavailability. Those dosed with 1200 mg weekly were found to

have 13.2% lower clearance compared to the other dose groups. Additionally, the Daily RPE study had 23.3% lower bioavailability when compared to RIFAQUIN study.

Conclusions: Our study is the first to show that the *AADAC* rs1803155 (AA) polymorphism is associated with low rifapentine clearance, leading to increased rifapentine exposure, although the size of the effect detected is unlikely to be of clinical significance Additionally, we found that rifapentine exposure was lower in HIV infected patients which is consistent with previous findings on rifamycin's. The patients in 1200 mg dose group were given the drug in less frequent dosing schedule which may have led to less pronounced auto-induction. The study effect detected is likely linked to differences in food pattern across the studies, highlighting the importance of standardising this aspect when studying PK of rifapentine.

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II-13: *Thomas Frank* LaTeX-based report writing: 10 years' experience from Sanofi's M&S group in Germany

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Objectives: The writing of population analyses reports fulfilling the specifications of submission readiness is a time-consuming process and highly subjective to human errors. In order to ease this process and diminish the likelihood of error we have been using LaTeX to write these reports. The objective of this poster is to share our concept and our latest 10 years' experience in using LaTeX to write population analyses reports.

Methods: The document preparation system LaTeX (TeX Live) has been in use internally for about 20 years to write population analysis reports. The templates were maintained and further developed over the years in order to enable newer functions and improvements of TeX Live, to comply with regulatory requirements, and to ensure simplification that allows less experienced LaTeX users to benefit from the template. The current template version is based on 'scrartcl' document class of KOMA-Script (TeX Live 2017 for Linux). It essentially consists of one master file that inputs multiple sub-files representing the textual content of each section of the report. Each file is provided with example text and clear guidance to allow modifications. In general, users only need to modify the sub-files to insert specific information on the analysis performed. Future-safe TeX Live packages like 'biblatex/biber' and 'glossaries' manage bibliographic data and/or definitions of terms/abbreviations. The rendition of one single PDF file, including creation of reference list and list of abbreviations proceeds automatically by using 'make' program. Our LaTeX template is maintained in an internal git repository that enables a shared and version-controlled update.

Results: Over the last 10 years, 28 reports have been issued in the corporate document management system, whereof 27 are part of Common Technical Documents (CTDs). Over the years LaTeX has remained open-source software and found to be very stable. The use of LaTeX-based report writing was found to facilitate the work not only of the author of the report, but also of the Quality Control (QC) reviewer and the coordination group responsible for the submission readiness of the report. For the author, one of the main advantages of using the LaTeX-based report is the easiness in insertion of tables and figures and the creation of the extensive appendices. High-resolution figures and tables can be inserted seamlessly by simple commands and the path to the files. Figures can be inserted in their native PDF format without resulting in an unnecessarily inflation of the size of the report source file or need for prior conversion of graphics file format. As a consequence, updating tables and figures becomes a much easier task. For the QC reviewer, the advantage of using LaTeX-based report lies on the fact that every step in the process is documented and reproducible. Finally, the document coordination group within Sanofi has also benefit from our LaTeX-based reports since there are never formatting issues or rework to be done. Adaptations due to changes in corporate layout guidelines can also be made very easily. In the past we have had some negative feedback from reviewers due to the fact that no MS Word version was available to allow review using 'track changes'. This issue was almost fully resolved by the advances of tools for commenting in PDF documents. For successful implementation of LaTeX in report writing the team should have at least one expert on the topic who offers comprehensive user support either individually or via channels, e.g., wiki pages, written user guides and regular tutorials.

Conclusions: Our concept for the template was developed in a way that proved to be simple enough to allow non experienced LaTeX users to benefit from it. The advantages of using LaTeX-based report writing

are found to overweight the few disadvantages. In general, our group has a very positive experience in using LaTeX-based report writing, and we tend to continue using it in the future.

II-14: *Sebastian Frechen* A technical concept of automatic PBPK platform (re-)qualification in the Open Systems Pharmacology Suite (PK-Sim® and MoBi®)

Juri Solodenko (1), Christian Diedrich (1), Sebastian Frechen (1), Jan-Frederik Schlender (1), Michael Sevestre (2), Rolf Burghaus (1)
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Objectives: The recently issued draft guideline on physiologically-based pharmacokinetic modeling (PBPK) by the European Medicines Agency (EMA) [1] demands the qualification of the intended use related to the PBPK platform for any type of simulation scenario (e.g. CYP3A4 inhibition, pediatric scaling in primarily renally cleared drugs, etc.) in regulatory submissions. Once such a type of scenario is qualified for its use, changes in the software platform (e.g. adjusted or extended model structure, changed parameterization of a model, etc.) require requalification. The objective was to develop a technical concept of automatic requalification of the type of scenario.

Methods: PK-Sim® as part of the Open Systems Pharmacology (OSP) suite [2] is a well-established PBPK tool widely used for more than a decade. It offers different structural models together with relevant physiological and molecular database information for PBPK modeling of small and large molecules in different animal species and human populations. MoBi® can directly use PBPK models created in PK-Sim® but is especially designed for the de novo construction, import, or extension of systems biology and pharmacology models in an (extendible) ordinary differential equation framework. Generally, a certain type of scenario consists of multiple simulations involving a variety of PBPK drug models. A technical concept of its requalification with every new software release was developed.

Results: For a specific type of scenario a software processable “Qualification Plan” is constructed semi-automatically. It consists of:

1. A minimal amount of information required to setup all simulations for the intended type of scenario in the Open Systems Pharmacology Suite. This includes the information on primary input parameters (e.g. molecular properties like molecular weight, lipophilicity, etc.), additional model building step (e.g. instructions for incorporating a-posterior knowledge via estimation of unknown parameters from clinical data) of the respective PBPK drug models involved in the particular scenario. Additionally, required input for system parameters (e.g. demographic characteristics) is provided.
2. A list of differences between used model values and default values stored in the physiological and molecular OSP databases for the combination of inputs above.

The execution of the “Qualification Plan” produces:

1. A report on the evaluation of the individual PBPK drug models with experimental data sets (i.e. standard goodness-of-fit plots, visual predictive checks).
2. A comprehensive qualification report for the type of scenario including a predefined set of qualification measures assessing predictive performance (e.g. root-mean-square deviation (RMSD), geometric mean fold error (GMFE), etc.) and charts (e.g. observed vs. predicted data for selected pharmacokinetic parameters - e.g. AUC ratio, Cmax ratio, etc.).

Conclusions: A technical concept is presented to produce comprehensive (re-)qualification reports automatically. This enables an efficient assessment both for sponsors and regulatory bodies and thereby provides full traceability and transparency of all steps. (Re-)Qualification reports can be generated and distributed for every for every new version of the Open Systems Pharmacology Suite.

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II-15: *Matthias Frei* Distinguishing myelosupressive response of a paclitaxel –radium-223 combination using a model-based analysis of an individual cross-over phase-Ib trial in cancer patients with bone lesions

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Objectives:

Concomitant treatment with radium-223 and paclitaxel is a potential treatment for cancer patients with bone metastases; the agents have potentially synergistic mechanisms of action. Both agents are myelosupressive, and the increased risk for myelosuppression of the combination needs to be assessed. Objective of this analysis was to evaluate the potential interaction of concomitant paclitaxel and radium-223 treatment on the myelosuppression with a PK/PD modeling approach. Data were obtained with an individual cross-over design in a phase Ib study, enabling to separate the myelosuppressive effect of the 2 drugs, and allowing a small sample size.

Methods:

Neutrophil data were obtained from an open-label, multicenter, nonrandomized phase Ib study in cancer patients with bone metastases. Patients received up to 7 cycles of chemotherapy, with 90 mg/m^2 paclitaxel IV per week in a 3-week-on / 1-week-off regimen, administered as per local standard of care. Starting with the 2nd cycle, subjects received up to 6 cycles 55 kBq/kg radium-223 IV, 1 injection every 4 weeks. Main observation period was the first 12 weeks with neutrophil observations obtained twice per week.

A previously developed semimechanistic PK/PD model[1] was used, describing the time course of paclitaxel-induced myelosuppression. This model had been adapted for monotherapy with radium-223.

The paclitaxel and radium-223 models were combined to evaluate the myelosuppression under concomitant treatment with radium-223 and paclitaxel in the current phase Ib study.

Models were implemented in NONMEM 7.3.

Results:

There were 12 patients included in the analysis, all of which completed treatment cycles 1 – 3. Following refinement of parameter values, the previously developed model adequately described the time course of paclitaxel-induced myelosuppression in cycle 1. In the combined radium-223 and paclitaxel model, the drug effect was implemented as Bliss Independence model[2]. The model adequately described the drug-induced myelosuppression in cycles with combined treatment. Model parameter estimates were consistent with previously reported results from paclitaxel studies[1]. The study design proved to be suitable for the separation of the myelosuppressive effect of the 2 drugs with a small number of subjects. Simulations of a typical patient, treated according to the analyzed study design, showed that after cycle 3 of treatment, the additional effect of radium-223 results in an additional decrease of the absolute neutrophil count at the nadir by ~10% of the baseline value when co-administered with paclitaxel, versus paclitaxel alone.

Conclusion:

A combined radium-223 and paclitaxel myelosuppression model – with the drug effect implemented as Bliss Independence model – described the neutrophil time course adequately well in cancer patients with bone lesions. The study design proved to be suitable for the separation of the myelosuppressive effect of the 2 drugs with a small number of subjects. Simulations of a typical patient, treated according to the analyzed study design, showed that after cycle 3 of treatment, the additional effect of radium-223 results in an additional decrease of the absolute neutrophil count at the nadir by ~10% of the baseline value when co-administered with paclitaxel, versus paclitaxel alone.

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II-16: *Svetlana Freiberga* Understanding sources of variability: The variability attribution plot

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Objectives: Understanding and explaining sources of variability in the data is a significant component of any analysis. Clinical trial data with its many levels of hierarchy, such as country, center, patient, visit, sample, and so on, is particularly complex. Fortunately, nonlinear mixed effect models (NLMEM) have proven to be well suited to handle this complexity, and they have become the quasi-standard for pharmacometric trial data analysis. However, it can be challenging in practice to understand the complex interactions of parameter variability, residual variability, covariates and the non-linear function. A parameter on the logit-scale with large estimated variability might still only contribute to a small fraction of the variability in the response and another one with a low BSV magnitude might translate to a significant driver of response variability.

The objective of this work was therefore to introduce a novel model visualization that allows attributing the different constituents of response variability dynamically.

Methods:

Derivation: Following the law of total variance, the model variability model was first split into residual unexplained variability (RUV) and between-subject variability (BSV). Using a general formula for the decomposition of variation [1], the BSV was then further decomposed by successively conditioning the remaining variability on groups of random effect parameters. The resulting exact but analytically intractable expression was approximated by considering a linearization of the NLMEM. From this approximation, the conditional variance expressions were derived analytically.

Implementation: The visualization method was implemented using NONMEM, PsN, and R. First, PsN is used to generate an augmented NONMEM control stream extracting the necessary derivative information for the linearization. R is then used to calculate the conditional variability expressions and plot each variability component as stacked ribbon versus the independent variable.

Evaluation: The visualization was evaluated by applying the method to a set of 31 published model and assessing the plausibility of the resulting plots.

Results: A novel model visualization to attribute different sources of variability was implemented and applied to a set of 31 models. In its current implementation, the method applies to all continues-type data models in NONMEM.

For a one-compartment model with first-order absorption for warfarin [2], as an example, the visualization shows how during the first couple of minutes variability is almost entirely driven by the BSV in absorption rate. This is followed by a phase where variability is dominated by the variability in distributional volume and, finally, a phase with a successive increase in the importance of clearance BSV. The additive RUV in this model shows as a factor with varying contribution, only 5% in the absorption phase and up to 25% in the terminal phase.

For models with a full random effect covariate model (FREM)[3], the approach allowed visualizing the impact of covariates at different time points. Furthermore, by varying the conditioning order, it was also possible to highlight different aspects of the variability composition, such as either the contribution from each parameter or from all PK and PD parameters together.

Conclusions: This new visualization provides insights into the importance of the many sources of variability in an NLMEM. The gained understanding can guide model building decisions and assist in communicating model assumptions to non-modelers.

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II-17: *Nicolas Frey* Bridging from Intravenous to Subcutaneous Formulation of Tocilizumab for Optimal Dose Regimens in Systemic Juvenile Idiopathic Arthritis

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Objectives:

Tocilizumab (TCZ) is a recombinant humanized anti-human IgG1 monoclonal antibody directed against the interleukin-6 receptor (IL-6R) that binds specifically to both soluble (sIL-6R) and membrane-bound IL-6R, thereby inhibiting IL 6 mediated signaling. The intravenous (IV) TCZ formulation is approved in the European Union, United States, and Japan for adult rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), and polyarticular juvenile idiopathic arthritis (pJIA). The subcutaneous (SC) formulation of TCZ is approved for the treatment of RA and giant cell arteritis.

The mechanism of action for TCZ is well understood, and the efficacy has shown to be well correlated with the target saturation of IL-6 receptors. The exposure-response relationships between TCZ steady-state C_{trough} ($C_{trough,ss}$) and PD/efficacy parameters were well established for the IV formulation for sJIA indicating that TCZ steady-state C_{trough} was a good surrogate of the target saturation. Hence, bridging from IV to SC formulation for TCZ in sJIA was based on exposure achieved at $C_{trough,ss}$. Utilizing the population PK models developed for the IV formulation for sJIA in combination with prior knowledge on the SC formulation from the adult RA population, SC dose regimens that were able to achieve similar ranges of $C_{trough,ss}$ as the IV dose regimen were recommended for sJIA patients.

The objective was to confirm the adequacy of the SC dose regimens of TCZ proposed for sJIA using a pharmacometrics approach.

Methods:

Prior to study start, SC regimens 162 mg Q10D (< 30 kg) and QW (≥ 30 kg) were recommended for sJIA patients in JIGSAW118, a phase Ib, open-label, multi-center study to investigate the PK, PD, and safety following TCZ SC administration in patients with sJIA aged 1 to 17 years. An interim analysis was planned at Week 14 to confirm that the proposed SC regimens would achieve similar $C_{trough,ss}$ compared with the approved IV regimens. At interim analysis, the $C_{trough,ss}$ achieved following 162 mg Q10D (< 30 kg) and QW (≥ 30 kg) were at the higher end of the exposure predicted prior to study start for all patients across the entire body weight range. Bioavailability was estimated to be around 95% based on data from 28 patients available at the time of interim analysis, which was higher than that observed in adult RA patients (~80%). This resulted in higher than anticipated $C_{trough,ss}$ following the 162 mg Q10D SC regimen, and the SC regimen for patients with BW < 30 kg was changed to 162 mg Q2W SC. For patients with BW ≥ 30 kg, the $C_{trough,ss}$ were similar to that achieved following IV administration, so the 162 mg SC QW regimen was considered adequate and was not changed.

At the end of the 52-week study, TCZ serum concentrations from JIGSAW118 (25 patients < 30 kg [162 mg SC Q10D (n = 8) or Q2W (n = 17)] and 26 patients ≥ 30 kg [162 mg SC Q2W]) were pooled with TCZ IV data

from TENDER (Phase 3, randomized, double-blind study in sJIA patients aged 2 to 17 years with 46 patients < 30 kg [12 mg/kg IV Q2W] and 43 patients ≥ 30 kg [8 mg/kg IV Q2W]). A total of 1710 quantifiable serum samples from 140 sJIA patients were analyzed using a two-compartment model with parallel linear and Michaelis-Menten elimination. Covariate analysis was conducted to identify covariates that may influence disposition of tocilizumab in sJIA patients. Graphical analyses were conducted to evaluate effects of tocilizumab SC exposure on pharmacodynamics biomarkers, key safety parameters, and exploratory efficacy measures.

Results:

The study met its primary objective as more than 95% of sJIA patients in JIGSAW118 achieved $C_{trough,ss}$ higher than the 5th percentile achieved with TCZ IV in TENDER. In addition, changes over time in pharmacodynamic biomarkers sIL-6R, CRP, and ESR were similar following both SC regimens, and to those achieved with the approved IV regimens. Graphical exposure-safety analyses confirmed there was no apparent association between exposure and occurrence of any SAEs, AEs in "Infections and Infestations" SOC, or neutropenia AE. Results of graphical exposure-efficacy analyses for sJIA patients following the SC regimens demonstrated that variability in TCZ exposure was not associated with the variability in efficacy parameters Juvenile Arthritis Disease Activity Score 71 and Childhood Health Assessment Questionnaire–Disability Index scores.

Conclusions:

Results of these analyses confirmed that tocilizumab 162 mg SC Q2W (< 30 kg) and QW (≥ 30 kg) regimens are adequate for the treatment of sJIA.

II-18: *Fiona G. Gao* Prediction of human pharmacokinetics of subcutaneously administered depot formulation using MBPK model

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Introduction: Subcutaneous depot formulations are increasingly being utilized, especially for the administration of biopharmaceuticals. However, the mechanism of drug release and absorption as well as lymphatic uptake at subcutaneous site remains unfathomed. In our project, we focus on Physiologically based pharmacokinetic (PBPK) modeling for subcutaneously administered depot formulations. For the current study, a commercially marketed depot formulation (Provera®) was selected. Feasible *in silico* pharmacokinetic (PK) simulation for depot formulations requires a suitable *in vitro* release method. A dialysis-based setup – the Dispersion Releaser (DR) has been successfully applied to test the drug release from nanosized drug carriers [1, 2] and was used to investigate the release kinetic of Provera®. Before the construction of an intricate PBPK model, a mechanism-based pharmacokinetic (MBPK) model was built in order to facilitate an exploratory research to determine the impact of release, absorption and lymphatic uptake on PK profile. Here, we try to demonstrate the influence of relevant changes in release emphatically.

Objectives:

- Integrate *in vitro* parameters, i.e. release and diffusion rate, into a MBPK model to estimate the *in vivo* drug performance
- Verify the MBPK model by evaluating the *in silico-in vivo* correlation
- Investigate the impact of release relevant parameters on PK profile

Methods: The release of Provera® in a buffer system simulating subcutaneous environment was investigated using the patented DR technique. The drug release kinetics was described with the Reciprocal Powered Time (RPT) model. The diffusion of free drug molecules was analyzed by performing agarose gel assay. For this purpose, a validated method was modified to comply with the lipophilic drug molecules [3]. A MBPK model was built in STELLA software integrating the release relevant parameters and diffusion rate. Additionally, other PK or physiological parameters were either determined using PK modeling in Phoenix WinNonlin or taken from literature.[4-6] The model was verified by comparing the *in silico* simulated PK profile with the clinical data of Provera®. At the same time, the local sensitivity analysis was utilized for evaluating the impact of release relevant parameter on PK simulation output.

Results: The cumulative drug release fraction (F) fitted using RPT model:
where m and b were release relevant parameters with the value of 0.14 and 0.92, respectively. The cumulative diffusion fraction of free drug molecules was determined as 8.75% per hour. Applying these parameters to the model, PK profile was simulated and precise prediction of C_{max}, T_{max} and AUC was achieved. With the local sensitivity analysis, it was confirmed that release relevant parameters were essential for the built MBPK model. The 10% change of release rate exerted significant influence on C_{max} and T_{max}. Also the AUC was not affected by this change.

Conclusions: The drug release test using DR technique as well as the agarose gel based diffusion assay were useful tools for the determination of formulation parameters. They enabled a MBPK simulation of

subcutaneously administered drug products. The multiple compartment MBPK model was capable of predicting the *in vivo* release, absorption, distribution, and elimination of Provera® with high precision. The next step will be to develop this MBPK model into a detailed PBPK model to simulate the *in vivo* PK for subcutaneous depot of biopharmaceuticals.

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II-19: *Silke Gastine* Nonparametric Pharmacokinetic-Pharmacodynamic Modelling of Posaconazole

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Objectives: As one of the latest triazole antifungal agents Posaconazole shows activity against both *Aspergillus* spp. and *Candida* spp. [1]. Posaconazole is widely used in treatment and prophylaxis of invasive fungal infections.To monitor pharmacodynamics of antifungal substances in-vivo, it has been shown, that the polysaccharide galactomannan is a valid PD surrogate regarding aspergillosis [2]. Being part of the fungal cell wall, galactomannan is released during fungal growth and thus declines with the drugs effect. Although current guidelines suggest therapeutic drug monitoring to ensure adequate Posaconazole exposure [3], there is some uncertainty about therapeutic targets for both prophylaxis and treatment of established disease.

Methods: The PKPD of Posaconazole was investigated for the treatment and prophylaxis of invasive pulmonary aspergillosis due to *Aspergillus fumigatus* in persistently neutropenic rabbits [4]. A total of 46 rabbits were included in the study. They were divided into four arms: healthy (n= 6), prophylaxis (n= 9), treatment (n= 16) and control (n= 15). The healthy arm received a single 20 mg/kg dose of Posaconazole with subsequent pharmacokinetic sampling. All other groups received pulmonary inoculation either the day before treatment or four days after the start of prophylaxis. Antifungal therapy consisted of Posaconazole at 2, 6, and 20 mg/kg of body weight orally. No Posaconazole was administered in the control group, but inoculation was performed as a control for both the treatment and the prophylaxis setting.

To evaluate the pharmacodynamics, galactomannan levels were collected every other day during the study. Nonparametric PKPD model building was performed using the Pmetrics Package in R [5]. In a first step the structure of the PK model was explored. Up to three compartments as well as linear and non-linear elimination were tested. Subsequently, a PD model describing galactomannan was added. Separate PD models as well as simultaneous modelling were tested to depict galactomannan levels in the treatment, prophylaxis and control group.

Results: A one-compartment model with first order oral absorption from a depot compartment and linear elimination best described the pharmacokinetics of Posaconazole (r^2=0.934, individual predictions).

Final parameter means (SD) of the PK part of the model were: Clearance 0.60 (0.57) L/h, central volume of distribution 117 (98.6) L. Ka was fixed to 0.35 1/h, derived from estimations with PK only.

The pharmacodynamic effect of Posaconazole plasma concentrations on galactomannan levels was best described by dynamic Hill-functions reflecting growth and kill of the fungus (r^2=0.864, individual predictions).

Final parameter means (SD) of the PD part of the model were: population maximal growth reflected by galactomannan index (GAI) 6.58 (1.73) , hill coefficient for growth 196 (98.4), hill coefficient for kill 55.8 (88.2), maximum rate of growth 0.03 (0.02) GAI/h, maximum rate of kill 1.97 (1.69) GAI/h, C50 for growth 0.19 (0.13) mg/L , C50 for kill 3.99 (1.95) mg/L, inital galactomannan concentration 0.1 (0.1) GAI.

Conclusions: The nonparametric population PKPD model adequately describes Posaconazole pharmacokinetics and its pharmacodynamic effect on fungal growth, reflected by galactomannan. It is possible to simultaneously predict the efficacy of Posaconazole PKPD for prophylaxis and treatment, as well as the evolvement of galactomannan levels in the control group. This model provides a further insight into drug exposures, that are important for the prevention and treatment of invasive pulmonary aspergillosis.

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II-20: *Florence Gattacceca* Pharmacokinetic-Pharmacodynamic (PKPD) model of Rilpivirine in HIV-1-infected patients treated with the single-tablet regimen rilpivirine/tenofovir/emtricitabine

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Objectives: Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor widely prescribed for the treatment of HIV-1 infection both in naïve and pre-treated patients. An important inter-individual pharmacokinetic (PK) variability has been observed [1] and RPV trough plasma concentrations (Ctrough) has been shown to be correlated with the virologic response [2]. However, until 2017, no study of RPV pharmacokinetics and pharmacodynamics (PD) had been published in a routine follow-up context. The only information available in the Summary of Product Characteristics came from the studies performed by the sponsor in drug development clinical trials (phase I healthy patients and phase III highly selected HIV-infected patients). The first aim of our study was to describe the RPV PK and its variability in adult HIV-infected patients in a routine follow-up context [3]. Second, we aimed to develop a PKPD model to establish dose-concentration-response relationships for future treatment optimization.

Methods: We conducted a multicenter, retrospective and observational study in patients treated with the once-daily RPV/tenofovir disproxil fumarate (TDF)/ emtricitabine (FTC) regimen. Ambulatory patients for which plasma RPV concentrations were determined within the context of routine therapeutic drug monitoring (TDM) were included from November 2012 to November 2015. Plasma HIV RNA load (VL), CD4 cells counts (CD4) and drug-resistance associated mutations were collected at baseline and during the monitoring. The population PK-PD (PopPKPD) analysis was performed with NONMEM VII software using Pirana interface 2.7.0. For the PD analysis, the individual Ctrough were predicted based on the PopPK model using Bayesian approach. A HIV dynamics model was developed to estimate the effect of RPV concentrations both on the infection rate of CD4 by the virus and on the VL [4,5].

Results: A total of 379 HIV-1 infected patients and 779 RPV plasma concentrations were included for the PopPK analysis. Overall, 24.4% of observed individual Ctrough were below the 50 ng/ml minimal threshold currently recommended. A one-compartment model with first-order absorption best described the data. The estimated fixed effect for plasma apparent clearance and distribution volume were 9 L/h and 321 L respectively, resulting in a half-life of 25.2 h. The inter-individual variability of clearance was 30.3 %.

Sixty-four treatment-naive patients were included in the PKPD analysis. We analyzed 492 data for VL and 487 for CD4 from initiation of treatment until a maximum of 2.5 years later. The parameters of the model were the production rate constant of uninfected target cells (So), elimination rate constant of infected cells (δ), production rate constant of free virions (c), VL at baseline (VL_0), CD4 at baseline ($CD4_0$) and the RPV concentration producing 50% of the maximum effect (C_{50RPV}). δ needed to be fixed to previously reported value of 15.2 per month [6]. The interindividual variability (IIV) on δ, So and c were inaccurately estimated, and consequently fixed to zero. The resulting model led to well-estimated parameters (Relative Standard Error under 30%) and was qualified based on the goodness of fit plots. However, a bias associated

with an underestimation of the highest VL values at baseline was observed. The estimated value of C_{50RPV} (79 ng/ml) was close but higher than the currently acknowledged target RPV Ctrough value of 50 ng/ml.

Conclusions: Our results showed that half-life of RPV is shorter in routine clinical practice than reported in the Summary of Product Characteristics, associated to a higher risk of under-exposure, in line with the simultaneous PopPK study performed within the same context of routine TDM by another group [7]. The PD model suggested that the currently used 50 ng/ml RPV Ctrough efficacy target might also be under-evaluated. Altogether, our PKPD model advocates for an increase of the RPV dose. However, our PD model showed some limitations, with a bias in VL prediction. Consequently, alternate HIV dynamics models will be tested, incorporating more biological prior knowledge (about slow viral decline and proliferation, age effect on CD4, thymic output) and a direct effect of RPV Ctrough on VL [8].

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II-21: *Wei Gau* Viral Dynamics Model Predicts Clinical Efficacy in Hepatitis C Virus (HCV) Infected Patients Using Viral Kinetic Data from Phase 1 Studies

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Objectives: Grazoprevir (GZR, a protease inhibitor), uprifosbuvir (UPR, a NS5B inhibitor) and ruzasvir (RZR, a NS5A inhibitor) are direct acting antiviral agents for treatment of chronic HCV infection. Efficacy of these agents was tested as monotherapy in Phase 1 studies or as combination therapy in Phase 2 studies[1,2]. A semi-mechanistic viral dynamic model was developed to translate the viral kinetics data obtained from the short term monotherapy studies to the clinical outcomes after long term combination therapy.

Methods: Plasma HCV RNA time courses during and after treatment were collected in the monotherapy studies: 10 to 800 mg once daily (QD) of GZR for 10 days, 10 to 450 mg of UPR as single dose or QD for 7 days, or 10 to 120 mg QD of RZR for 5 days. In Phase 2 trials, the combination regimen of 100 mg GZR, 450 mg UPR and 60 mg RZR for 8, 12 or 16 weeks was evaluated. The HCV RNA data were collected at various time points from day 1 to end of treatment and the clinical efficacy endpoint was SVR12 rate, the proportion of subjects achieving sustained virologic response 12 weeks after the end of all study therapy.

The viral dynamics model was developed based on the previously published two strain model [3]. Uninfected cells were assumed to be infected with HCV (either wild-type or mutant) and new virus was produced from infected cells (either wild-type or mutant) which would go on to infect other uninfected cells. The drug effect was characterized as inhibiting the viral load production and/or increasing the infected cell death rate. Specifically, the effects of GZR and RZR were driven by the plasma concentrations while the effect of UPR was driven via an effect compartment. The model was simultaneously fit to all monotherapy data from each regimen component and parameters describing the viral dynamics system and drug effects were estimated.

The model was then used to simulate the clinical efficacy of combination therapy. The effect of HCV genotype (GT) and the presence of baseline resistance-associated substitutions (RASs) were also accounted for in the model.

Results: The maximum HCV RNA reduction following short term monotherapies ranged from nearly no reduction to ~4.5 log10 IU/mL reduction from baseline. The semi-mechanistic viral dynamics model described the HCV viral kinetics following monotherapy adequately. In Ph2 studies, HCV RNA in the majority of patients was below the limit of quantification at week 4. After including the combinational drug effect, simulated HCV RNA time courses agreed well with the observations from Ph2 studies. SVR12 rates in Ph2 studies ranged from 78% to 100%, varying between treatment duration, HCV GTs and presence of baseline RASs. After accounting for these baseline characteristics, the model was able to predict SVR12 rates reasonably well for each treatment arm.

Conclusions: By incorporating our current knowledge of HCV viral dynamics, baseline patient characteristic and pharmacodynamic data from short term Phase 1 monotherapy studies, the viral dynamics model was able to successfully predict the clinical efficacy outcomes in long term HCV combination therapy studies. This model can be used to predict efficacy of the described combination regimen under conditions that

were not studied clinically and could potentially provide a framework for extrapolation to other combination regimens.

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II-22: *Glenn Gauderat* Reversing resistance to anticancer treatment supported by pharmacokinetic/pharmacodynamic modeling of tumor growth kinetics in xenograft mice

Glenn Gauderat
Servier

Objectives:

The development of drug combination in oncology is a key domain for answering therapeutic need. For example, combination therapy can be used to overcome drug resistance. In this context, the standard of care drug A is a targeting drug approved for the treatment of Non-Small Cell Lung Cancer treatment (NSCLC). Unfortunately, about half of patients develop drug resistance within 10 months. Resistance-lifting drug S is a candidate to be administered in combination with the standard of care in order to reverse tumor resistance and drug B is a competitor drug targeting the same pathway. Using a Pharmacokinetic/Pharmacodynamic (PK/PD) modeling approach, the aim of the present study was to compare our candidate drug to the competitor, when administered in combination with the standard of care on a resistant NSCLC tumor model.

Methods:

Tumor growth kinetics were determined on SCID mice bearing human NSCLC xenografts resistant to the standard of care drug. Six treatment groups of 8 mice were used to compare drug combinations potencies: control, drug S in monotherapy, drug A in monotherapy, drug B in monotherapy, drug S + drug A and drug B + drug A. Two to 3 weeks daily oral administrations were initiated 18 days after subcutaneous inoculation of tumor cells. Both resistance-lifting drugs were measured in blood at two time points after two weeks of treatment. Extensive PK data from previous studies were used to determine the PK model structures and population parameters for both resistance-lifting drugs, while concentrations measured in the present study were used to estimate individual exposures through Bayesian estimation. Tumor volumes were measured daily during 60 days (including tumor relapse) and modeled using the Simeoni [1] tumor growth inhibition (TGI) model. Parameter estimation was performed using Phoenix® NLME™. The standard of care drug concentrations were not modeled since it was assumed that it did not exert any effect on its own. Resistance-lifting drugs potencies were estimated separately for each treatment group and compared both in monotherapy and in combination with the standard of care drug.

Results:

Although a high inter-individual variability was observed, individual blood concentrations of drug S and drug B were correctly described by the PK models developed previously. The PD model that best described the tumor volume data was a Simeoni TGI model with a linear effect model. Transit compartments and first-order rate constant of transit K1 were removed from the original model since they did not improve the model performance.

As expected, Drug S, A and B used as monotherapy had very little if any activity on tumor growth kinetics compared to controls. Monotherapy groups were fitted using tumor growth parameters estimates from the control group in order to get drug potency estimates in reasonable computation time. Drug S was more potent than drug A and drug B in monotherapy.

In combination, our candidate drug was two times more potent than the competitor, with tumor volumes predicted lower at the end of the treatment period. Interestingly, the tumor relapse data after combination therapies allowed estimating tumor growth parameters under combination treatment conditions that were considerably different from those estimated from the control group, with tumor growth being slower after relapse than for control group. Indeed, to estimate tumor growth parameters was mandatory to properly model the tumor volume in the combination treatment groups, with tumor growth rate being about 1.4 times lower for drug B + drug A and about 3.3 times lower for drug S + drug A compared to control.

Conclusions:

A PK/PD analysis allowed comparing two drug potencies when administered in combination with a standard of care drug. Besides being more potent that drug B, another unexpected asset of drug S was a reduced tumor growth rate after relapse. Now, it is unclear whether this difference in tumor growth parameters is due to the drug S itself or to the fact that a smaller tumor cell subpopulation remained at the end of the treatment period compared to drug B. The present study supports the benefit of tumor volume measurement after relapse to better characterize a drug activity.

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II-23: *Francois Gaudreault* Model based Phase 2 Dose Selection of BIIB059 in Subjects with Systemic and Cutaneous Lupus Erythematosus (SLE and CLE)

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Objectives: BIIB059 (anti-BDCA2) is a humanized, immunoglobulin G1 (IgG1) monoclonal antibody currently under development for treatment of SLE including CLE. BIIB059 is targeted against BDCA2, a receptor expressed on the surface of the human and non-human primate plasmacytoid dendritic cells (pDCs). The objective of this work was to select dosing regimens for BIIB059 in the ongoing phase 2 study (NCT02847598).

Method: Dose selection was performed using a stepwise approach including *in-vitro* and *in-vivo* data as follow: 1) Determination of *in-vitro* EC90 and IC90 values for human BDCA2 internalization and for interferon alpha (IFNα) inhibition in human whole blood assays; 2) Establishment of the relationship between EC90 and IC90 values for BDCA2 internalization and IFNα inhibition based upon *in-vitro* data obtained from 10 healthy human donors; 3) Estimation of *in-vivo* EC90 value for BDCA2 internalization using the population PK-PD model developed based upon phase 1 PK and PD (BDCA2 internalization) data in healthy volunteers and SLE subjects (NCT02106897); 4) Prediction of *in-vivo* IC90 value for IFNα inhibition using the *in-vivo* estimated EC90 value of BDCA2 internalization in humans and the *in-vitro* relationship established between BDCA2 and IFNα; 5) The final PK-PD model was used to perform simulations and select doses for inclusion in the phase 2 study which are expected to keep the concentration of BIIB059 above EC90 of BDCA2 internalization and IC90 IFNα inhibition.

Results: The estimated *in-vitro* EC90 and IC90 values for BDCA2 internalization and IFNα inhibition based upon average of 10 human donors were 0.051 µg/mL and 0.67 µg/mL, respectively. The relationship between BIIB059 concentration and BDCA2 was well characterized by a two compartment PK model with linear and non-linear elimination and an indirect response pharmacodynamic model with stimulation of Kout (rate of elimination). The estimated *in-vivo* EC90 value for BDCA2 internalization from the population PK-PD model was 0.9 µg/mL. The estimated *in-vivo* IC90 IFNα inhibition based upon *in-vitro* relationship between the EC90 of BDCA2 and IC90 of IFNα and *in-vivo* EC90 values estimated based upon the PK-PD model in SLE patient was 11.7 µg/mL. The doses selected for the phase 2 study were: 50, 150 and 450 mg SC Q4W as based upon simulations using the final PK model.

- The low dose of 50 mg SC Q4W is expected to achieve plasma concentrations sufficient to maintain 90% BDCA2 internalization (EC90 = 0.9 µg/mL), for the duration of the dosing interval.
- The middle dose of 150 mg SC Q4W is expected to achieve plasma concentrations similar to or in excess of the calculated IC90 for IFNα (11.7 µg/mL) for the majority of the dosing interval.
- The top dose of 450 mg SC Q4W is expected to achieve Cmin levels similar to 3-fold of the calculated IC90 for IFNα inhibition (i.e. >35.1 µg/mL)

The safety margin compared to 450 mg SC Q4W dose based upon 6 month toxicological studies in cynomolgus monkeys is 25-fold and 48-fold for AUC and Cmax, respectively. In addition, the exposure of 450 mg SC Q4W is also expected to be lower than 20 mg/kg IV dose administered in phase 1 study and hence the selected doses for phase 2 study are considered safe and tolerable.

Conclusion: *In-vivo* and *in-vitro* data in combination with pharmacometric approaches allowed the selection of phase 2 doses for BIIB059.

II-24: *Kamunkhwala Gausi* methodological characterization of qt/qtc in children with severe malaria anaemia receiving arthemether-lumefantrine preceded by quinine

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Objectives: Oral artemether-lumefantrine (AL) is often administered shortly after the completion of parenteral quinine in the treatment of hospitalized children with severe malaria in sub-Saharan Africa. However, quinine is associated with QT-prolongation on the electrocardiogram and lumefantrine has similarities to halofantrine, an antimalarial known for QT-prolongation. Little is known whether this effect is increased by sequential administration of lumefantrine preceded by quinine. Cardiotoxicity of antimalarial medicines cannot be easily tracked in areas where antimalarial drugs are often used (e.g. Sub-Saharan Africa), as these are often resource poor settings where ECG monitoring might not be available and identification of high risk patients might therefore be challenging. The aim of the study was to develop methods to characterize the cardiac safety (using QT/QTc) of artemether-lumefantrine when preceded by quinine in treating malarial cases among children in Malawi and identify risk factors of QT-prolongation

Methods: Secondary data from a clinical trial on “intermittent preventive therapy post-discharge (IPTpd)” was analysed. The trial recruited 133 children with severe malaria anaemia aged 4–59 months. Electrocardiograph assessments were conducted 12 hours after the last quinine dose which was immediately prior to the first AL dose (0 hour), and again 6 hours and 62 hours later. The trial had two arms: those administered 6 quinine doses and those administered 5 quinine doses. A Fixed effect model(FEM) and a linear mixed-effects model (LMEM) were derived and adopted to analyse the effect on the QT-interval of AL preceded by quinine. The LMEM was based on simulated lumefantrine concentration over time profiles parameter from a similar study in Uganda. Model estimation was based on Stochastic Approximation of Expectation Maximization (SAEM) and covariate selection was based on stepwise forward and backward elimination, while Akaike Information Criteria (AIC) was used to compare the models.

Results: Administering quinine followed by LA lead to a linear regression-corrected QT (QTc)of > 500 ms in 5 children administered 6 quinine doses. The trend of the QTc across the three time points was that most patients started with an elevated QTc (mean of 464.8 ms) due to the effect of quinine, but the mean QTc decreased at 6 hours to 461.16 ms (95%-CI: 457.63 - 464.69 ms) then starts to rise at 62 hours 462.58 (95%-CI: 458.43 - 465.28 ms). The participants administered 6 quinine doses (n =50) had a pronounced increase in QTc between 6 to 62 hours compared to the 5 quinine doses (n = 71). The parameter estimates and corresponding 95% confidence interval from LMEM were 465 (462, 468) ms for the intercept and -0.35 (-0.748, -0.072) ms for slope indicating that even with an increase in concentration of LA, QTc decreases with time. The model identified 4 covariates that were affecting QT-interval of the patients: sex, number of quinine dose, haemoglobin and feeding condition. LMEM model offered the best fit to data with the lowest AIC = 2570.797.

Conclusions: The co-administration of LA did not maintain the high QTc values caused by quinine, but

female patients receiving 6 quinine doses were at high risk of QT-prolongation. Similarly, anaemic undernourished patients are also at a relatively high risk of QT-prolongation.

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II-25: *Anna Georgieva Kondic* Integrated novel modelling framework for evaluating the efficacy and cost effectiveness of novel pharmaceutical agents in stroke prevention

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Objectives: There were two main, related, objectives of our study. The technical goal was to create a comprehensive individualized and transparent modelling framework that could be easily used to evaluate the potential for economic differentiation of new drug candidates against existing therapies. An example application of particular interest was the evaluation of a novel anticoagulant being considered for stroke prevention. This example comes from a therapeutic area that requires large and costly outcome trials and can benefit from informed early go/no go decisions. Additionally, this modelling study evaluated the handling, user-friendliness, and efficiency of model development and readability of the resulting model as compared to existing tools.

Methods: A Markov cohort [1] economic model described in Verhoef at al [2] compares three different factor X molecules and coumarin derivatives in the settings of the UK and the Netherlands. The model considers a uniform group of patients with atrial fibrillation who can experience a variety of cardio-vascular (CV) events, such as myocardial infarction, systemic embolism, ischaemic stroke, transient ischaemic attack, as well as bleeding events, each of which carries a certain risk for disability or death. The comparison between the different therapies is based on their published efficacy, safety, effect on quality of life and costs. An initial model using the mean parameters as presented in [2] was first implemented in heRo3 [3], a web-based tool that runs the R-based economic modelling package heemod [4]. The Markov formulation of the model in heRo3 required a large number of health states which, combined with the different therapies made it cumbersome to characterize the different combinations of incidents, especially if we were to consider different patient sub-populations. The model becomes difficult to understand by the different stakeholders (reviewers, non-modeller partners). A more intuitive representation of such a model is enabled by the Discretely Integrated Conditions and Events (DICE) methodology [5], where states are not mutually exclusive but each patient simultaneously carries several attributes characterizing the patient's health state. This DICE methodology forms the basis of the R based Health Economics Modelling (RHEM) Framework, developed for this work. The example model was implemented, simulated and analyzed in the RHEM Language using the DICE methodology.

Results: We developed the RHEM Framework and subsequently formulated the example model in the new RHEM Language. This allowed us to represent all required features for an example compound and implement the desired target product profile while also considering the uncertainty associated with early clinical development and account for the variability in the patient population. The resulting RHEM model code is well readable and intuitively understandable, supporting efficient model building and understanding by reviewers. The simulations in the RHEM Framework reveal the separation between different groups of patients based on their covariate characteristics and suggest that enriching for the responder patients can increase the probability of success for a clinical development program. In addition, the deterministic and probabilistic sensitivity analyses point out to the most sensitive parameters in overall model predictions. As such, the new RHEM modelling tool can be used to inform future clinical trials to gather the data necessary to inform the sensitive parameters.

Conclusions: The RHEM modelling framework, as applied to the novel anticoagulant agent demonstrates that it is possible to allow for efficient and user-friendly definition of Health Economic models that integrate diverse information (pharmaceutical properties, efficacy, safety, patient characteristics and health resource utilization) in order to characterize the value proposition of new therapeutic molecules and target populations who may benefit from new treatments. The resulting RHEM modelling approach is intuitive to understand, can scale up to large problems and can be applied to different therapeutic areas in order to inform clinical development and registration strategy for molecules under development. As the underlying RHEM simulator is based on the DICE methodology, different modelling types, including Markov models and Partitioned Survival models [6] can be supported and the modeler can choose the methodology that is most useful for a particular problem and therapeutic area.

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II-26: *Eva Germovsek* An exposure-response model relating nicotine plasma concentration to momentary craving across different nicotine replacement therapy formulations

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Objectives: Tobacco use is estimated to cause over 7 million avoidable deaths yearly [1] by increasing the risk of developing cancer, causing chronic obstructive pulmonary disease, accelerating cardiovascular diseases, increasing the risk of infectious diseases and insulin resistance, etc. Tobacco use is therefore a major individual and also a global public health problem, thus it is vital to reduce its use. Nicotine replacement therapy (NRT) medications reduce craving for nicotine, and hence facilitate smoking reduction and cessation [2]. Our aim was to improve the understanding and to quantify the relationship between nicotine plasma concentrations and momentary craving across different NRT formulations. By developing a pharmacokinetic-pharmacodynamic (PKPD) model we were also aiming to quantify the between-subject variability and to identify possible formulation-dependent differences. Additionally, since the momentary craving was assessed using two different scales (specifically, a 4-category scale, and a 100 mm visual analogue scale (VAS), i.e. a 101-category scale), we also aimed to link the results from both scales.

Methods: Data available for analysis originated from 17 different studies, including four NRT formulations: mouth spray, lozenge, gum and patch. Subjects in the studies received NRT medications only and were instructed not to smoke. Existing formulation-specific population pharmacokinetic (PK) models and individual PK parameter estimates were utilised to obtain dynamic nicotine PK profiles for each individual. If individual PK parameter estimates were unavailable, the population estimates were used. A linear direct-effect model was used to relate nicotine plasma concentration to craving (reduction), and formulation-specific slopes were investigated. To link the observations from the two different scales, a joint model was developed for the VAS scale based on a bounded-integer model concept [3], where a probit-based model provides the probability of each observation. For the scores from the 4-category scale, we estimated the probabilities, in order to be able to link them with the VAS scores. NONMEM 7.3 (ICON Development Solutions, Ellicott City, Maryland) with the Laplace approximation was used to obtain the likelihood.

Results: The data included 1,077 adult subjects with median (range) age 28 (18-55) years and weight 72 (49.4-112.8) kg, smoking 20 (5-50) cigarettes per day for 12 (1-45) years. The subjects provided 41,424 momentary craving observations, 15,424 of which were measured with the 4-category scale, and 25,922 with the VAS. In this analysis, the slopes for all oral NRT formulations were estimated to be similar (i.e. -0.24 mL/ng, -0.20 mL/ng, -0.14 mL/ng for mouth spray, lozenge and gum, respectively), but the slope for patch was estimated to be lower (-0.04 mL/ng). The score of 1 on the 4-category scale was estimated to represent scores 0-27 on the VAS, score of 2 as 28-65, score of 3 as 66-91, and score of 4 as 92-100 on the VAS.

Conclusions: A linear direct-effect PKPD model was developed and related nicotine plasma concentrations to momentary craving from four different NRT formulations. A new methodology, bounded integer model was for the first time applied to link observations from two separate pharmacodynamic endpoint scales. Future work will include, for example, testing non-linear models to describe the concentration-effect relationship, evaluating a possible delay in the onset of the effect, assessing the influence of other

covariates (such as markers of nicotine dependence), and perhaps including a tolerance development or other time dependency in the PKPD relationship.

Disclosures: EG, MCK and MOK declare no conflicts of interest; AH, JJPR, ÅW, PS and AV are (former) employees of subsidiary companies of Johnson & Johnson.

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II-27: *Anais Glatard* Population pharmacokinetic model of amisulpride for individual dosing in psychiatric patients

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Objectives: The atypical antipsychotic drug amisulpride is used orally at a wide range of doses (50-800 mg daily) for the treatment of negative and positive psychotic symptoms [1]. Amisulpride is mainly eliminated unchanged via the kidney and the elimination half-life is around 12h. This low membrane permeability drug is a substrate of Permeability Glycoprotein (P-gp) and of Organic Cation Transporters (OCT1, OCT2) responsible for the tubular secretion of the drug [2]. A low fraction of the dose (12%) is metabolized by the cytochrome P450 3A4 (CYP3A4) in two inactive metabolites. Because amisulpride may provoke important dose-dependent adverse effects (e.g. hyperprolactinemia, extrapyramidal symptoms) and because a dose-therapeutic response relationship has been demonstrated, therapeutic drug monitoring of this antipsychotic is strongly recommended [3]. The aim of this study was to describe the pharmacokinetic profile of amisulpride in psychiatric patients and to detect genetic and non-genetic sources of variability in order to better individualize doses.

Methods: The population pharmacokinetic analysis was performed by use of NONMEM® based on plasma samples from a cohort of hospitalized patients or followed in ambulatory care at the Department of Psychiatry of the Lausanne University Hospital. Seventeen single nucleotide polymorphisms (SNP) of the OCT transporters, P-gp and nuclear receptors that regulate OCT transporters were selected for analysis and genotyped using the Cardio-MetaboChip (Illumina) containing customized SNPs for pharmacokinetic genes when an informed consent was obtained from patients. With the use of a one-compartment model with first order absorption and integrating a known bioavailability of 48%, the influence of demographic (age, sex), clinical (body weight, body mass index, smoking status, creatinine clearance estimated by the Cockcroft-Gault (CLCG) or the Salazar-Corcoran formula (CLSZ)) and genetic characteristics as well as comedications (inhibitor or substrate of OCT transporters, inhibitor or substrate of P-gp, inhibitor of CYP3A4) on amisulpride clearance and volume of distribution was quantified.

Results: A total of 517 amisulpride plasma concentrations from 245 patients (18-91 years) were collected for the analysis. Systemic clearance (CL) was 45.7 L/h (Relative Standard Error RSE 4%) with an inter-individual variability of 23% (RSE 20%) and the volume of distribution (V) was 846 L (RSE 10%) with 44% of inter-individual variability (RSE 29%). The absorption rate constant was 0.4 h^{-1} (RSE 25%). Univariate analysis revealed a significant linear relationship between amisulpride CL and CLSZ, body weight, age and smoking ($p<0.001$) as well as between V and age ($p=0.02$). No significant influence of the 17 single nucleotide polymorphisms of transporters and nuclear receptors was found on amisulpride elimination. Multivariate analysis with forward selection ($p=0.05$) and backward deletion (Bonferroni-adjusted $p<0.003$) revealed an amisulpride CL increase of 25% in a 120-kg patient compared to a 75-kg patient and a CL decrease of 55% for a 80-year patient compared to a 40-year patient. Body weight and age explained 8% and 58% of the inter-individual variability of amisulpride CL, respectively. Body weight and age were correlated with CLSZ (Pearson correlation coefficient $r^2=0.41$ and $r^2=-0.68$, respectively) and had less missing data than CLSZ (38%) explaining that CLSZ was not retained. In addition, the influence of age on V was not retained.

Conclusions: The present study showed an important influence of body weight and age on amisulpride concentration and highlight the importance of a personalized dosage adjustment especially in elderly individuals with a low body weight. This model may be implemented in a Bayesian tool for dosage adjustment to predict amisulpride concentrations in psychiatric patients. Finally, the present model will be used to characterize the relationship between amisulpride concentrations and weight gain during the treatment.

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II-28: *Nathalie Gobeau* Model-based informed screening of antimalarial combinations

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Introduction: Malaria is treated with combination therapies in order to minimize resistance. However, resistance is unavoidable and therefore the hunt for new treatments must continue. The objective of MMV is to develop new combinations that achieve 95% cure rates 28 days after a single-dose administration. Currently, the 28-day cure rates (ACPR28) of individual new molecules do not exceed 80%. Hence combinations must be identified so that 2 compounds together lead to a higher cure rate than each one individually. There are currently 8 antimalarial new molecules in the MMV portfolio which have already shown promising efficacy as monotherapy in humans – either in Controlled Human Malaria Infection (CHMI) studies or patient trials. From the large number of potential combinations of these candidates, the most promising ones need to be determined and progressed into late stage development.

Objectives: MMV aims to develop a strategy to screen a large number of combinations and select the most promising ones, i.e. the most likely to achieve the same efficacy with a single dose the as the current treatments which require three daily doses.

Methods: Individual compounds progress through drug development by going through a series of pharmacological models and by using PKPD models to identify the PKPD relationship and refine it at each stage. The first model is in SCID mice which are engrafted with human red blood cells and infected with *P. falciparum*, the most life-threatening malaria parasite specific to humans (1). The compound is administered at different doses when the parasitemia levels reach a predefined threshold. Blood concentrations and parasitemia are monitored for up to 2 months. A PKPD model is built in which the killing rate of the drug is related to its blood concentration by a sigmoidal Emax model - or a more complex model such as a turnover model, if needed. The second pharmacological model is a CHMI study where healthy volunteers are infected with *P. falciparum* and the drug is administered when parasitemia reaches a level which will not cause symptoms (2). Blood concentrations and parasitemia levels are measured for up to one month. Doses tested are subtherapeutic in order to determine the full PKPD relationship and in particular the minimum inhibitory concentration (MIC), the concentration below which parasites recrudesce. Finally, the compounds are tested in small cohorts of patients at different doses, high enough to not put the patients at risk.

Results: To screen combinations, a PBPK-PD model is generated to predict in humans the time-course parasitemia and calculate the clinical endpoint ACPR28, by using:

- The knowledge of the behavior of each compound in healthy volunteers or patients as monotherapy for both the PK and PD.
- The estimation of a possible interaction between the compounds in humans based on in vitro metabolism data and PBPK modelling: the PBPK model for each compound is validated with the human data – in patients if available or in healthy volunteers; the effect of the interaction on the PK profile of each combination partner is predicted by PBPK based on their victim and perpetrator properties.
- The estimation of the pharmacological interaction in SCID mice: several dosing regimens of the compounds as combination and monotherapy are tested. The general pharmacological interaction

model (3) is applied to combine the existing monotherapy models and include a possible shift in Emax and EC50 due to the interaction between the drugs. This approach is general and can be adapted to more complex models, such as turnover models if needed. The shift estimated with the SCID dataset is then assumed to be the same in humans. The values of Emax and EC50 are, however, not translated from animals: the latest information obtained for the compounds as monotherapy – in challenge volunteers or patients - is used.

The example of the combination of MMV048 and DSM265 will be used for illustration purposes.

Conclusion: 12 combinations will be tested this year. It is expected that the current strategy will be able to identify at least the combinations which will lead to an ACPR28 higher than the ACPR28 of each individual agent, and at best allow to rank the different combinations according to their predicted ACPR28. This would then help prioritize the combinations that would progress into the CHMI study to confirm the predictions before going into patients.

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II-29: *Nele Goeyvaerts* Population Pharmacokinetic/Pharmacodynamic of a Toll-Like-Receptor 7 (TLR7) Agonist that Induces IP-10 and ISG15 in Cynomolgus Monkeys

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Objectives: TLR7 agonists stimulate the innate immunity by inducing cytokines and interferon-stimulated genes (ISGs) to trigger an antiviral or antitumor effect. The aim was to develop a pharmacokinetic/pharmacodynamic (PK/PD) model for an oral, small molecule TLR7 agonist that characterizes the plasma exposures and type I interferon (IFN)-dependent innate immune response in healthy cynomolgus monkeys. To this purpose, two PD biomarkers were considered: IFN-γ-inducible protein 10 (IP-10) and IFN-stimulated gene 15 (ISG15). A secondary objective is to use mathematical models to interrogate the presence and interplay of amplification, receptor downregulation and circadian rhythm[1-5], physiological processes which are known to be involved in this pathway.

Methods: Plasma PK data were pooled from 7 monkey studies, involving 1714 plasma concentrations from 126 monkeys with doses up to 15 mg/kg and at different regimens. IP-10 plasma concentrations (n=1673) were available from 110 monkeys and ISG15 microarray data (n=773) were available from 50 monkeys. Dose was implemented in the model as per-kg basis with monkey weights ranging from 2.2 to 6 kg. The data were analyzed by a non-linear mixed effects modeling approach implemented in NONMEM V7.3.0[6]. Observations below the lower limit of quantification were accounted for by using the M3 method[7]. IP-10 and ISG15 were modeled sequentially based on individual PK estimates. Indirect response models with linear versus E_{max} stimulation on the production rate constant (k_{in}) were tested. Model selection was guided by the objective function value, diagnostic plots, standard error of parameters, evaluation of condition number, shrinkage, and visual predictive checks.

Results: Exposures increased in a greater than dose proportional manner. A three-compartment model with saturable pre-systemic target-mediated drug disposition (TMDD)[8]-like elimination, transit absorption, first-order distribution to 2 peripheral compartments, and first-order elimination from central compartment, was shown to adequately describe the pharmacokinetics of the TLR7 agonist in cynomolgus monkeys. The TMDD mechanism is novel for small molecule TLR7 agonists, pointing to possible pre-systemic TLR7 engagement in the gut-associated lymphoid tissues and liver, which was also suggested as the mechanism of GS-9620, another compound of this class[9]. Based on the mean population estimates, the fraction of drug absorbed increased from 2.6% at 0.05 mg/kg, 3.1% at 0.5 mg/kg, 4.0% at 1 mg/kg, 19.7% at 6 mg/kg, to 38.9% at 15 mg/kg. There was no evidence of time-dependent PK with multiple dosing. Females displayed faster absorption and higher bioavailability. The indirect response model used to describe the ISGs (IP-10 and ISG15) incorporated signal transduction using transit compartments. The driver for the stimulation of k_{in} of both IP-10 and ISG15 were slope functions of plasma concentration with an exponent estimated. An E_{max} model did not result in a statistically significant better fit. Therefore, the model with slope function was deemed as the most parsimonious given the available data. Inclusion of circadian rhythm and feedback did not significantly improve model fit. Further experiments and data are needed to demonstrate these processes conclusively.

Conclusions: A novel semi-mechanistic population PK/PD model has been developed for a small molecule TLR7 agonist in cynomolgus monkeys that could prove useful for other TLR7 agonists as well. Inclusion of

saturable pre-systemic TMDD adequately described the nonlinear pharmacokinetics. Stimulation of the innate immune response, as measured by the induction of ISGs (IP-10 and ISG15), was adequately described using an indirect response model with a slope function. The model will be used to translate PK/PD from monkey to human to inform dose setting for antiviral hepatitis treatment.

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II-30: *Antonio Goncalves* Modelling hepatitis B kinetics in mice treated by a novel TLR-7 agonist, alone or in combination with entecavir

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Objectives: Current antiviral treatment against Hepatitis B virus (HBV) rely on nucleoside analogues (such as entecavir, ETV) and are largely effective in reducing viral load levels and limiting disease progression. However these treatments do not eradicate virus and therefore they need to be taken lifelong to present virus resurgence. The main obstacle to cure is the fact that the virus is able to escape from the immune response, via the production of a large amount of subviral particles (SVPs) coated with HBs-antigen (HBsAg) that act as a decoy for the immune response [1]. In order to stimulate the immune response, a promising strategy is to use a toll-like receptor 7 (TLR7) agonist. Stimulation of TLR7 receptors indirectly induces the production of IFN-α and cytokines and stimulates antigen presentation [2]. Thereby, TLR7 agonists contribute to the organization of both innate and adaptive immune responses. Here we aimed to use a viral dynamic model to characterize for the first time the antiviral response during treatment with a TLR7 agonist used alone or in combination with ETV.

Methods: We used data collected by Hoffmann-La Roche in a mouse model [3]. A total of 118 animals were analyzed, treated with either a placebo (n=24), ETV (n=6), TLR7 agonist (n=76), or the combination of both (n=12) at various dosing regimen and for period of 6 to 9 weeks of treatment. HBV DNA (viremia), HBsAg (surface antigen) and anti-HBs (antibodies against HBsAg) were weekly measured across all studies. We developed a viral dynamic model that describes the interplay between virions, SVPs and antibodies. Indeed, infected cells produced virions and subviral particles in a large excess. We hypothesized that TLR7 agonist may induce the production of anti-HBs. However, a low amount of anti-HBs may be rapidly occupied by binding to virions and SVPs and forming immune complexes, and such immune complex-associated antibodies can be difficult to detect. The immune complexes may be eliminated and cause an extra decay of their kinetics, or may eventually reform viral particles. We estimated the percentage of reduction of the production on virions and SVPs and the stimulation of anti-HBs levels.

Results: A biological model of chronic hepatitis B, integrating the role of anti-HBsAg in virus elimination, could successfully reproduce all the observed data in both monotherapy and combination groups. With this model, we showed that ETV efficiently blocked HBV DNA production (ε=99.9999%) but had no effect on HBsAg or anti-HBs titers. In contrary, the TLR7 agonist has shown a triple mechanism of action, whereby production of both virions and SVPs were successfully blocked. Production of virions could be reduce 93.80 % for and 99.70% at the dose of 100 mg/kg weekly (QW) and every other day (QOD) respectively, whereas reduction of the production of SVPs could be reduced by 99.70% up to 99.97%. In addition, our model suggested that the treatment led to an increase in anti-HBs concentrations, thereby allowing for further reduction of viremia and HBsAg titers on the long run. Eventually, a model assuming a Loewe additivity of ETV and the TLR7 agonist in reducing virion production could well reproduce the data observed during combination therapy.

Conclusions: The model provides a novel framework to analyze the effect of immunomodulatory drugs that is consistent with destabilization of viral production and stimulation of antibody production, which may

contribute as combination partner in the perspective of a cure. Future analyses including other drugs in combination with TLR7 agonist and clinical studies are needed to confirm the potential of this therapeutic class.

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II-31: *Ignacio Gonzalez* Exploration of different scenarios using a drug exposure-response model of Lurbinectedin

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PharmaMar

Objectives:

There are different strategies to validate a PKPD model. However, only when the model is able to describe and predict the data correctly and additionally has been validated, it is appropriate to perform simulations in order to explore a new dose range, new schedules, etc. Other types of simulations are also relevant as a way to measure the effect of the covariates either on the dependent value (e.g. concentrations, tumor size, absolute neutrophil count) or in the PK or PD parameters.

Nowadays, performing this type of simulation is not complicated, and there are many useful software available. However, these simulations have an inconvenient, especially when NONMEM is used. Simulation parameters (e.g. doses and times of administration, number of cycles and sampling times) have to be pre-established before simulations are run, and cannot be modified during the simulation exercise. Moreover, these simulation parameters can be modified only once the results of the simulation are analyzed. Such modifications may entail repeated changes in the database until the final result is achieved, which is highly time-consuming and not efficient.

PhM-TSim (PharmaMar Trial Simulator) is a new tool aimed at speeding up this type of simulations where the knowledge of the subject's condition at present is needed to simulate the next subject's condition. Evaluating subject's condition after the last drug administration, PhM-TSim is capable to decide the dose regimen of the subsequent drug administration, which may be the same or a reduced one. Dose delays, omissions or administration of new therapies, such as growth colony stimulation factor (G-CSF), red blood cells and/or albumin transfusions, can also be considered.

The objective of this work is to present PhM-TSim as a new tool that implements changes in the database automatically, based on predefined per protocol re-treatment criteria. PhM-TSim combined with longitudinal drug exposure-response (DER) models is a valuable tool to assess scenarios for dose selection in future clinical trials.

Lurbinectedin is a drug under clinical development with several phase II and III trials ongoing/planned. The most relevant toxicity associated to lurbinectedin is the decay of absolute neutrophil counts (ANC), and is used as an example of the implementation of PhM-TSim.

Methods:

A DER model for ANC was developed and validated for the purpose of this work. Different simulation scenarios were planned in order to measure the capability of PhM-TSim when adjusting the dose (e.g. reduction, delay) to avoid serious toxicities during consecutive lurbinectedin administrations.

The lurbinectedin PKPD model was a 3-comparmental model with lineal kinetics (either distribution or elimination) combined with a DER model for ANC based on the one proposed by Quartino, and adapted by

Fernandez-Teruel, with transit compartments and feedback effects on mean maturation time and proliferating cell pool, which was suitable for describing the time course of neutrophils.

NONMEM 7.3 was used to perform the simulations, while R (v. 3.4.1) and R Studio® (v. 1.01.143) were used to build the data sets, graphical analysis and dose adjustment.

Results: For each scenario, a total of 100 subjects and a maximum of ten cycles were simulated. A univariate analysis of the covariates included in the PKPD model showed the real impact of the covariate in the subject's condition.

Conclusions: In all the scenarios simulated, PhM-TSim was able to first evaluate every subject's condition, and then, if necessary, to delay, reduce lurbinectedin administration or even withdrawal from the clinical trial. The versatility of PhM-TSim also allows the use of G-CSF or any other strategies predefined per protocol at the re-treatment criteria. The impact of a due covariate on subject's condition may not be the same after first drug administration than along the whole treatment, due to adjustments in dose regimen to manage toxicities. PhM-TSim shows a better description of the PD along the treatment than common simulations that do not consider dose adjustments, and ultimately can be implemented in simulations of DER efficacy models, to account for such dose adjustments that affect subject's outcome in the clinical field.

II-32: *Kosalaram Goteti* Drug-disease model describing the effect of intraarticular injected sprifermin on cartilage thickness measured by magnetic resonance imaging in osteoarthritis patients

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Objectives:

Sprifermin, a recombinant human fibroblast growth factor 18, is under development for the treatment of knee osteoarthritis (OA) [1]. OA is characterized by loss of cartilage thickness. The objective of this analysis was to develop a drug disease model based on the magnetic resonance imaging (MRI) data measuring knee cartilage thickness in osteoarthritis patients.

Methods:

24 months data were used for this analysis that originated from a Phase II trial (FORWARD study). All subjects were planned to receive 4 cycles (each consisting of 3 weekly injections) of intraarticular (i.a.) treatment with sprifermin or matching placebo at intervals of 6 months. A total of 595 subjects were randomized in equal allocations to one of 5 treatment groups:

- 4 cycles of 100 µg sprifermin/injection,
- 2 cycles of 100 µg sprifermin/injection alternating with 2 cycles of placebo,
- 4 cycles of 30 µg sprifermin/injection,
- 2 cycles of 30 µg sprifermin/injection alternating with 2 cycles of placebo,
- 4 cycles of placebo.

Pharmacokinetic blood samples were collected pre-dose and 2 hours after the last dose of each cycle. Population analysis using NONMEM software was performed to identify potential longitudinal dose-exposure-response patterns. Cartilage thickness in total femorotibial joint compartment, as well as lateral and medial femorotibial compartments, as measured by MRI were selected for analysis. A base drug disease model for each of the three MRI measurements was developed and this base model consisted of two components; one for the disease progression, which in the present case also includes placebo-disease model since there was no arm with absence of treatment, and one for the drug effect. As serum sprifermin concentrations were below the lower limit of quantitation following the i.a. injection, the exposure model was replaced with a simplified first order input and output equation (Bateman-type function) for a description of the so-called 'driving force' profile, modified through a driving force-effect model. The driving force-drug effect component was described using a linear relationship and the drug-effect profile was added onto the disease progression. The driving force-effect relationship was also explored as a Emax-type model. The models were assessed using goodness of fit plots and visual predictive checks (VPCs). Potential influence of covariates was assessed on drug effect, including age, race, geographical region, gender, minimum joint space width at baseline, Kellgren-Lawrence grade, malalignment, and bilateral/unilateral OA using a stepwise covariate model search (SCM) with a $p < 0.01$ and 0.001 for inclusion/removal in the forward/backward steps.

Results:

MRI data for three measurements from 496 subjects with OA from 5 dosing arms were available.

Best fits were obtained with a linear model describing the placebo-disease effect, a Bateman-type driving force profile, and a linear model for the driving force-effect relationship.

Emax-type models for the description of the driving force-effect relationship instead of a linear relationship, did not result in a significant improvement from the base model.

The SCM did not find any covariates that would pass the set significance criteria for any of the three MRI measurements. Therefore, the base models were considered the final models, and adequacy was confirmed using VPCs.

The final model of the MRI cartilage thickness in total femorotibial joint estimated a baseline thickness of 1.79 mm (95%CI: 1.76/1.81) with 0.258 mm additive inter-individual variability (IIV), slope of placebo-disease progression was -0.0165 mm over 2 years (95%CI: -0.026/ -0.0072) with 0.056 additive IIV. Driving force was given by Dose*(Time/T_{max})*exp(-Time/T_{max}), with T_{max} estimated at 12.3 months (95%CI: 6.7/17.8), and slope of drug effect was 0.00042 mm/driving force unit (95%CI: 0.00029/0.00055). The results for medial and lateral MRI cartilage thickness were consistent.

Conclusions:

A placebo-disease and drug disease model was developed for sprifermin for MRI measurements of total femorotibial joint, lateral femorotibial compartment, and medial femorotibial compartment cartilage thickness. This model will be useful for understanding the gain in cartilage thickness as measured by MRI with different treatment schedules and dose levels of sprifermin in future drug development for osteoarthritis.

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II-33: *Verena Gotta* Modelling urea clearance in pediatric and young adult patients on chronic hemodialysis

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Objectives: Delivered urea dialytic clearance (KD) can be predicted from a standard mechanistic equation in adult patients on chronic hemodialysis, based on prescribed blood flow (QB), dialytic flow (QD) and in vitro mass-transfer coefficient for urea of the filter (KoA) [1,2]. It has been suggested that KD is however underpredicted in pediatric hemodialysis patients using this equation [3]. This could be caused by significant differences in dialysis prescription between pediatric and adult patients [3], leading to greater difference (bias) between *in vitro* determined and *in vivo* observed KoA in pediatric patients. For example, this may be explained by low and *in vitro* untested QB and/or QD [4,5]. The aim of this analysis was to improve the prediction of *in vivo* KoA and thus KD in children on maintenance hemodialysis.

Methods: A two-compartment urea kinetic model previously developed in adults [2] was scaled based on physiologic understanding of kinetic parameters to pediatric patients (total urea distribution volume = total body water [6], distribution clearance scaled by cardiac output [7,8]), with between-subject variability (BSV) assigned to KoA. The model was fitted using NONMEM (FOCE with interaction) to a dataset comprising pre- and post urea concentration samples of 923 pediatric and young adult patients aged 1-29 years (2676 HD sessions in total, with up to 3 hemodialysis sessions (occasions) per patient). Stepwise covariate model building was used to evaluate the association and relationship of prescription parameters with individual *in vivo* KoA estimates. Nested models were compared by the likelihood ratio test, based on the decrease in objective function value (ΔOFV, α=0.05). The mean relative prediction error (MrPE) in post-HD urea concentrations was further calculated with 95% confidence intervals to assess the bias in population predictions for age groups 1-6, 7-12, 12-18, and 19-29 years.

Results: Increased QD/QB ratio was the parameter most strongly associated with a bias between reported *in vitro* KoA of the filter and individual estimated *in vivo* KoA (ΔOFV: -359, $p<0.001$). A bias of only -4.4% (95% CI: 2.5-6.2%) was estimated at a QD/QB ratio of 2 (reference ratio used in adults), with a linear increase to +114% at a QD/QB ratio of 5 (median ratio used in infants [3], slope estimate: 0.379 (95% CI: 0.34-0.42)). Inclusion of QD/QB ratio as a covariate removed bias observed with QB and QD, and reduced the MrPE in post-HD concentrations largely in children (decrease from 58% (35-81%) to 6% (-9-22%) in children 1-6 years). Inclusion of session duration, filter properties (i.e. low-flux vs high-flux) and ultra-filtration rate could further improve the model fit.

Conclusions: Children on chronic hemodialysis are commonly prescribed much higher QD/QB ratios than adults, which are usually not tested *in vitro* resulting in the lack of characterization of filter performance for these settings. Although *in vitro* determined filter KoA is assumed to be a constant, our data shows that this is not the case under *in vivo* conditions, with largest *in vitro-in vivo* KoA deviations in youngest patients. Our new model allows prediction of urea dialytic clearance from a range of pediatric specific prescription parameters. The model may also serve to predict drug clearance in pediatric hemodialysis patients.

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II-34: *Sebastiaan Goulooze* Supervised item response theory modelling improves prediction of iatrogenic withdrawal in children

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Objectives:

Item Response Theory (IRT) modelling is a multivariate data analysis technique, which is increasingly used in pharmacometrics to analyse data from questionnaire-based clinical assessments [1]. Because IRT is essentially an unsupervised technique, the derived latent variable will not selectively quantify the condition of interest in all situations. For example, the clinical assessment of iatrogenic withdrawal syndrome (IWS) in children includes many items that are also affected by other conditions, such as disease, pain and undersedation. The latent variable obtained by IRT modelling of such data cannot be expected to selectively quantify IWS severity [2]. We therefore developed a supervised implementation of IRT [3] to analyse item-level data from IWS assessments in children [4].

Methods:

Data were obtained during the clinical validation of the Sophia Observation withdrawal Symptoms (SOS) scale, which is a 15-item scale to assess IWS in critically ill children [4]. In addition to SOS scores, the IWS severity was judged by trained nurses on a numerical (integer) rating scale called NRS withdrawal, which ranges from 0 (no IWS) to 10 (worst IWS possible). The NRS score represents the expert opinion, taking into account all contextual factors of the patient and was used as the gold standard during the validation of the SOS scale. With supervised IRT (sIRT), the item characteristic curves (ICCs) of each item were estimated by setting the latent variable to equal the NRS withdrawal score.

Subsequently, these ICCs were fixed and individual posthoc estimates of the latent variable were estimated from the item-level data in the absence of NRS score. We compared the ability to predict NRS withdrawal scores using either the posthoc estimated sIRT latent variable, the total SOS score, or the latent variable estimated with the unsupervised IRT model.

Results:

In the sIRT model, two-parameter item characteristic curves (ICCs) were used for 9 of the 15 items. For five items, a three-parameter ICC was used that adds parameter for the maximum probability of observing the symptom: 61.3% for *Agitation*, 46.7% for *Inconsolable Crying*, 19.9% for *Grimacing*, 68.2% for *Sleeplessness*, and 21.7% for *Diarrhea*. The probability of experiencing *Sweating* was best described with a five parameter biphasic ICC. The contribution of each item to the total test informativeness ranged from 1.5% for the *Tremor* and *Diarrhea* items to 17.1% for the *Motor Disturbance* item.

Local minima were often encountered when fitting an unsupervised IRT model to the withdrawal data, often with unrealistic parameter estimates as a result. The final unsupervised IRT model contained two-parameter ICCs for all items, as more complicated models failed to adequately converge. In linear models

to predict the NRS score, the sIRT latent variable performed better than the total SOS score (AIC of 5636.4 versus 5789.8). The unsupervised latent variable performed worse as a predictor of the NRS score, with an AIC of 5792.0.

Conclusions:

As many of the behavioural and symptomatic items of paediatric questionnaire-based assessments can be caused by different conditions, an unsupervised IRT model of the item-level data of such assessments might inadequately quantify the condition of interest. In our example, we leveraged context-specific information in a sIRT approach to guide the estimated latent variable from the SOS scores towards IWS. Compared to the unsupervised IRT, the sIRT approach resulted in increased model stability and an improved prediction of iatrogenic withdrawal from SOS score data.

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II-35: *Silvia Grandoni* Evaluating the inclusion of the particle size distribution in the lung dissolution model of a WB-PBPK model to describe the pharmacokinetics of inhaled polydisperse drugs.

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Objectives: evaluating the impact of the particle size distribution of a polydisperse powder of inhaled drugs (compared with a monodisperse powder with particle size equal to the Mass Median Aerodynamic Diameter (MMAD)) on the lung and plasmatic concentration-time profiles derived with a WB-PBPK model.

Methods: administration of inhaled drugs was added to a previous developed and validated WB-PBPK model structure [1]. In particular, the lung was modelled considering its two main anatomical regions, the central (C) and the peripheral (P) one; each of these was further divided in three sub-regions to take into account the main physiological process occurring when a drug is inhaled, i.e. deposition, clearance, dissolution and absorption [2]. Hence, the resulting lung model comprises the following compartments for both the C and the P parts: the undissolved state compartment (to consider the amount of drug which deposits in the respiratory system), the dissolved state compartment (which represents the pulmonary Epithelial Lining Fluid (ELF), in which the drug dissolves) and the lung tissue. Each region is characterized by a different volume and surface and a different level of perfusion, since the C region is connected to the systemic circulation while the P region is connected to the pulmonary circulation.
Regarding the processes in which the inhaled compounds are involved, the dissolution was modelled with the Nernst-Brunner equation [3], the mucociliary clearance was included as acting in the C region only, as a first order process and the absorption was described as a first order process with an absorption rate constant depending on the surface area of the region and on the permeability of the drug.
The model was implemented in MATLAB™ in two versions which differ in the dissolution modelling only. The first version is structured as described above and considers all the particles as monodisperse and characterized by the MMAD. The second, structured to consider the particle size distribution (obtained as a fractional mass distribution from the impactor filter analysis), differs in the structure of the undissolved state compartments, which are divided in 9 sub-compartments (for both the C and P region), each of them containing an amount of monodisperse solid drug characterized by a certain diameter (taken as the mean diameter from those filtered from each filter section). The amount in each sub-compartment dissolves with a different rate due to its different particle size, following the Nernst-Brunner equation.
A series of intratracheal experiments were simulated in rats to compare the two models.
Different particle size distribution scenarios were reproduced, ranging from the realistic bell-shaped profile centred around the MMAD, to non-realistic U-shaped profiles in which the smaller and/or the larger particles are more represented. To compare the two versions of the model in similar conditions the particle size distributions were generated with the same MMAD.

Results: simulating with the U-shaped particle size distributions, deviations from the plasmatic and lung concentration-time profiles obtained using the MMAD only occur, in particular, the presence of earlier and higher plasma peaks is observed. Simulating with the bell-shaped distribution the differences are negligible.

Conclusions: with the here proposed WB-PBPK model, deviations from the PK profiles obtained considering the particles as monodispersed and represented by their MMAD occur only in some cases of non-realistic

U-shaped distributions. Considering that actually the particle size distribution of the powders is typically bell-shaped and centred around the MMAD, the use of the MMAD only in the dissolution model seems to be, in this context, sufficient to describe the powder particle size in the lung dissolution process.

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II-36: *Hans Peter Grimm* PK Projections for Therapeutic Proteins in Entry Into Human Studies: Roche pRED Experience From 2004 to 2016

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Objectives:

Defining safe and pharmacologically meaningful doses for clinical studies at Entry Into Human (EIH) strongly relies on human PK projections based on pre-clinical PK and other information for the molecule and to some extent inference from similar molecules. Here, we present the results of a review of the methodology and the success of model-based prediction of exposures for EIH studies in Roche pRED (pharma Research Early Development) between 2004 and 2016.

Methods:

Information on models for human PK prediction was systematically collected for all 21 Roche pRED-sponsored monotherapy projects with therapeutic proteins achieving EIH between 2004 and 2016. Where a prediction model was available prior to EIH, its quality was assessed based on Cmax and AUC. For this, the reported models were implemented in Berkeley-Madonna and simulations run reflecting the design of the clinical studies. Predictions were considered adequate when they were within 2-fold of the averaged observed values (NCA) for >90% of the size-weighted cohorts. Where several prediction scenarios were used in parallel, the model predicting the higher exposure was used for comparison with observations.

Results:

Models for human PK prediction were available in 18 of the 21 projects investigated. In all these cases, the models were built on PK data from non-human primates (cynomolgus monkeys) and allometrically scaled using fixed exponents: exponent of 1 for volumes and ranging from 0.75 to 1 for clearance. In several cases (5/18) two parallel prediction scenarios were given with the intention of providing upper and lower bounds for the prediction; this included one case in which the PK of a typical monoclonal antibody was used for the prediction. 10 out of the 18 prediction models were linear 2-comparment models. Another 5 models captured the impact of target-mediated drug disposition (TMDD) by a non-linear clearance function to which scaling was equally applied. In the remaining cases more complex models were used.

More than 80% of the predictions of Cmax and roughly 55% of predictions of AUC were found within 2-fold of observations. In seven of the 10 cases where a linear model was used this was found to be adequate. Where TMDD was predicted, this was found adequate in 6 of the 8 cases. In the remaining cases, TMDD was either not anticipated at all or under-estimated by these models.

Conclusions:

This systematic review of model predictions for human PK predictions for therapeutic proteins shows that the relatively simple allometric scaling from the PK in non-human primates provides useful and robust projections for the planning of EIH studies. Challenges, where they appeared, were most often related to the TMDD and its projection, exacerbated by the very low doses used in some studies with compounds for

cancer immunotherapy. This underlines the need in developing robust methods to improve confidence in mechanistic and/or physiologically based models for human PK prediction.

II-37: *Ana-Marija Grisic* Towards a comprehensive PK/PD model of infliximab in inflammatory bowel diseases, with support of prior knowledge

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Objectives:

Introduction of the anti-tumour necrosis factor α monoclonal antibody (mAb) infliximab (IFX) brought about a revolution in the treatment of inflammatory bowel diseases (IBD), offering an efficacious therapeutic option for patients unresponsive to conventional treatment. However, a high variability in response rate has been reported, with up to 60% of the IBD patients losing response to IFX over time. Previously, the loss of response has been related to low IFX plasma concentrations [1]. To our knowledge, IFX concentration-effect relationship in IBD has not been comprehensively described by PKPD modelling, despite its potential to empower therapeutic drug monitoring and improve therapy success.

To gain more insight into the mechanisms underlying the loss of response and set the basis for improved therapy strategies we employed PKPD modelling approaches to analyse the dose-concentration-effect relationship.

Methods:

Clinical PK (IFX plasma concentrations) and PD (biomarker concentrations of C-reactive protein; CRP) data from IBD patients ($n_{patients}$ = 121) was gathered as a part of an investigator initiated trial at the outpatient clinic of the Medical University of Vienna. Patients were treated with 2-h IFX infusion of absolute doses between 100 and 1300 mg. The samples ($n_{PK\ observations}$=388, $n_{PD\ observations}$=339) were collected at mid-term between two maintenance infusions and at end of a dosing interval (0.6-12.4 weeks after last dose). For the data analysis R, NONMEM (7.3.0), PsN and Pirana were used. As a first step, a PK model was developed and the impact of covariates on interindividual variability (IIV) of CL investigated (considering statistical and clinical significance of available covariates). To compensate for the data sparseness, a previously reported PK model [2] was utilised, by informing PK parameter estimation using the $PRIOR functionality of NONMEM. For the covariate analysis, parameters informed by the prior model were fixed to the final estimates of the base PK model. In the next step, a sequential PKPD analysis was performed, by using the empirical Bayes estimates of the PK model. Simultaneous parameter estimation was performed as an evaluative step on the final base PKPD model. Performance of the model was thoroughly evaluated at each step of the model development process.

Results:

A 2-compartment disposition model with linear elimination (CL=0.266 L/d) resulted in adequate description of the PK data. Random effect parameters comprised of mixed proportional-additive residual unexplained variability (RUV) and IIV in V_1, V_2, CL and RUV. As only IIV in CL was estimable solely from the data, covariate effects on CL were investigated. Inclusion of anti-IFX antibody status, disease activity (serum albumin concentration), body weight and concomitant therapy with immunomodulators explained ~30% of IIV in CL and reduced IIV in RUV. The model exhibited a good performance as judged by standard diagnostics (incl.

simulation-based methods). As extension to incorporate the PD component and in accordance with the mechanism of action of IFX, indirect response E_{max} model with inhibition of CRP synthesis process adequately described the biomarker data. Baseline CRP (0.63 mg/dL), I_{max} (0.72), IC_{50} (2.04 mg/L) and proportional RUV were estimated from the data alone, the CRP degradation rate constant was fixed to correspond to known CRP half-life (19h) and estimation of IIV in baseline CRP and IC_{50} was supported by a prior model [3]. Values of all parameters were in plausible ranges and the model demonstrated a reliable predictive performance. Estimated IIV in baseline CRP and IC_{50} was very high (115 and 209 % CV, respectively). Even though ability of investigated covariates to explain IIV was limited, the covariate analysis identified potentially significant covariates to be: a history of prior surgeries, age at diagnosis and smoking status.

Conclusions:

Within the study, a well-performing population PKPD model of IFX in IBD was successfully developed. Moreover, influential covariates on PK and PD parameters, and thus subpopulations at risk (presence of anti-IFX antibodies, higher disease activity, higher body weight and absence of co-therapy with immunomodulators) were identified. The developed model will be further extended to account for other biomarkers and subsequently be used to investigate potential therapy strategies to increase therapy success (i.e. ameliorate remission rate).

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II-38: *Felix Hammann* Whole-body physiology pharmacokinetic modeling of flip-flop behavior of oral oxycodone solution in pediatric patients 5-16 years old

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Objectives: The semi-synthetic opioid analgesic oxycodone has in some trials exhibited flip-flop pharmacokinetics when administered as an immediate-release formulation [1]. We noticed the same phenomenon in an analysis of a trial of oral oxycodone solution (0.1 and 0.2 mg/kg) in patients 5-16 years old, and explored the underlying reasons using a whole-body physiological pharmacokinetic (PBPK) modeling approach.

Methods: The pharmacokinetic data are from a double-blind, randomized, dose-ranging study in pediatric patients 5 to 16 years old, hospitalized for medical and/or surgical conditions, and receiving morphine as a standard supplemental pain medication to evaluate pharmacokinetics, efficacy and safety of oxycodone 1 mg/mL solution versus placebo for pain. Patients were stratified into two age groups (5 to < 12 years, and 12 to 16 years) and randomized to receive either oxycodone 0.1 mg/kg, 0.2 mg/kg, or placebo every 6 hours for 18 to 24 hours according to a randomization ratio of 3:3:2. A total of 46 patients were enrolled in the active treatment group, with 1-8 samples taken per patient.

Population pharmacokinetic analysis was carried out using NONMEM (Version 7.4.1; Icon Development Solutions, http://www.iconplc.com, Ellicott City, MD, USA). The first order conditional estimation with interaction (FOCE-I) was used throughout all runs. PK-Sim and MoBi (version 7.0; Open Systems Pharmacology Suite Community, http://www.systems-biology.com/products/pk-sim.html) was used for PBPK modeling and simulation.

Results: The final population pharmacokinetic model is a one-compartment model with first-order absorption and elimination. Total body weight was included as a covariate on Vd and Cl. We estimated the elimination rate constant (kel) at 0.55 h-1, and the absorption rate constant (ka) at 0.14 h-1. As kel > ka, we noted the presence of flip-flop pharmacokinetics, i.e. elimination is driven by absorption. Possible reasons for this may be opioid effects on gastrointestinal motility (either from oxycodone or concomitant morphine treatment), and underlying medical and surgical conditions.

To see whether drug- or disease-induced changes in oral absorption can be held accountable for this, we created a PBPK model of oxycodone in adult patients using a middle-out approach from a clinical trial of oral oxycodone solution (0.2 mg/kg) [2], and published data on the physico-chemical and absorption / distribution / metabolism / elimination properties of oxycodone. The model faithfully depicted the historical adult data. We then proceeded to scale the PBPK model to the population of this trial, and noted absorption was predicted to be much faster than observed. Particularly, maximum concentrations (Cmax) and areas under the curve from 0-12h (AUC0-12h) were over-predicted, and time to maximum concentration (Tmax) was underpredicted.

By changing the release model of oxycodone to conform to a Weibull function parameterized from visual inspection, we were able to create a modified PBPK model that matches all three relevant secondary pharmacokinetic parameters. The Weibull function has been previously established as an alternative for

modeling time-dependent first-order release [3-5]. A similar approach was taken by Li et al. who used semi-mechanistical modeling using a Weibull function for oral absorption of oxycodone [1].

Conclusions: Oxycodone oral solution (0.1 and 0.2 mg/kg, respectively) exhibited flip-flop pharmacokinetics in pediatric patients aged 5-16 years. This may be due to slowed gastrointestinal transit because of opioid effects and/or underlying medical or surgical conditions. This phenomenon can be modeled with a middle-out approach PBPK model when slowed oral absorption is accounted for with a Weibull function. Future studies of oral oxycodone should be wary of flip-flop behavior when defining sampling points.

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II-39: *Niklas Hartung* A size- and location-structured model for pulmonary absorption, elimination and dissolution of an orally inhaled drug

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Objectives:

Pulmonary absorption of orally inhaled drugs depends on the deposition pattern, dissolution process, and mucociliary clearance. Especially for slowly dissolving drugs, the complex interplay of saturable dissolution and mucociliary clearance results in nonlinear absorption and particle size-dependency [1-2]. Several recently proposed pharmacokinetic models for pulmonary pharmacokinetics strive to describe these processes in mechanistic detail [3-5]. Mucociliary clearance has been resolved spatially by transit compartment models and dissolution by the Nernst-Brunner equation. However, all models simultaneously describing the impact of saturable dissolution and mucociliary clearance have considerably simplified one of these two processes. Indeed, it is difficult to formulate a compartmental model representing this interplay accurately. The present work aims to overcome this hurdle by describing pulmonary absorption in a partial differential equation framework in order to integrate these two mechanisms in full detail.

Methods:

We modelled the simultaneous effects of mucociliary clearance and saturable dissolution by a location- and size-structured population equation (a partial differential equation) [6]. The main quantity in this model is a location-and size-resolved density, from which amounts can be recovered via integration over the two structuring variables. Mucociliary clearance is resolved along a typical airway, parametrized from physiological airway data and a mucus velocity model [7]. Dissolution is described by the Nernst-Brunner equation, and saturation via an additional location-resolved dissolution compartment, from which systemic absorption takes place. Deposition patterns were simulated with the MPPD v2.11 software [8], assuming inhalation patterns and particle sizes as described in the respective publications.

Results:

The structured population model was solved numerically using the method of characteristics [9]. In this approach, we used a fixed location grid adapted to changes of mucus velocity along the airway, and a time-dependent size grid, depending on the saturable dissolution process. Model predictions were compared to two sets of clinical data on fluticasone propionate, a slowly dissolving inhaled glucocorticoid used for treatment of asthma bronchiale and chronic obstructive pulmonary disease: i) using the same dose, but different particle sizes [1] and ii) different doses, but the same particle sizes [2]. In both scenarios, the model was able to qualitatively reproduce the observed nonlinear absorption patterns.

Conclusions:

We demonstrated that a structured population model can be used to describe the complex interplay of mucociliary clearance and saturable dissolution, in particular particle size-dependent and dose-nonlinear absorption patterns. Representing the interplay of all major processes, this framework could be used to predict the pulmonary bioavailable fraction for arbitrary lung deposition patterns, to assess local uptake

profiles to eventually evaluate inhaled formulations and treatment schedules. Future work aims at confronting the model to other substances, as well as to include a more detailed physiological airway representation.

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II-40: *Emilie Hénin* Individual therapeutic monitoring strategy of a factor IX concentrate (OCTAFIX ®) for prophylaxis in patients with haemophilia B, using population modelling approaches

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Objectives:

Prophylaxis for haemophilia B is effective but restrictive and expensive. Knowledge of a patient's pharmacokinetic (PK) profile after infusion of factor IX is likely to be useful in clinical management. Management of haemophilia B has mostly been empirical so far to determine dosage, with a combination of outcome measures such as clinical bleeding phenotype and determination of trough level of factor IX (FIX) activity. However, inter-individual pharmacokinetic variability of FIX is large and PK-tailored personalized prophylaxis may help to adjust FIX activity at the correct level.

A prospective, open-label, multi-centre phase 2 study, PeKaFIX, has been conducted between July 2016 and August 2017, to evaluate, by rich sampling, the pharmacokinetics of a plasma-derived factor IX concentrate (OCTAFIX®, as a single IV injection at a dose of 75 IU/kg, after a wash-out period of at least 7 days) in patients with haemophilia B. Data from 3 other studies (YNE-201, YNE-202, YNE-203), performed between 1996 and 2005, in adult and paediatric patients with haemophilia B receiving OCTAFIX, were also available for model development.

The aim of this work was to analyse, using population modelling approaches, the factor IX activity profile after OCTAFIX administration, and to externally evaluate, on PeKaFIX data, the predictability of individual parameters and comparison criteria under several sparse sampling designs, in order to propose individual therapeutic monitoring strategy.

Patients & Methods:

Factor IX time-courses, measured in 45 adult and paediatric patients with moderate or severe haemophilia B, receiving single or multiple prophylactic OCTAFIX® administrations at doses ranging from 36 to 81 IU/kg, were issued from the previously conducted YNE-201, YNE-202 and YNE-203 studies, and were considered for model development.

Several scenarios, i.e. rich sampling (13 observations per individual, considered as the reference) and sparse sampling (3-4 observations at various time points), were considered to predict individual parameters

in the 14 patients issued from PeKaFIX study, and compared in terms of Time-to-reach FIX xx% (5, 4, and 3%) and predicted FIX levels at time T (48, 72, 96 and 120 hours after administration).

Results & discussion:

The data from 45 patients, previously considered in YNE-201, YNE-202 and YNE-203 studies, were used to successfully build a population pharmacokinetic model, giving a good description of factor IX kinetics after OCTAFIX® single and multiple administrations, in adults and children with severe or moderate haemophilia B. The proposed model is a two-compartment model, with allometric scaling on parameters, and a baseline FIX level presenting endogenous production of factor IX. Inter-individual variability was found on clearance, central volume and basal FIX level.

Compared to the reference scenario (using all 13 samples per individual), the better sparse scenario accounted for 3 samples at 0, 0.5 and 48 hours after administration: absolute difference in FIX predicted levels was in median within the population 0.7% at 48 hours, 0.5% at 72 hours; 0.3% at 96 hours and 0.2% at 120 hours. Reference time-to-reach 5%, 4% and 3% were predicted in median at 91, 103 and 119 hours respectively; the above-mentioned scenario differed from 4 to 5 hours to reference values, allowing an adequate estimation of the dosing interval required to maintain FIX level above a given threshold.

All evaluated sampling schemes based on 3 or 4 observations gave acceptable individual predictions in terms of FIX profile, predicted FIX level at a given time and in terms of time-to-reach a given FIX level. However, better predictive performance was obtained when sampling schemes included samples up to 48 hours over schemes up to 24 hours after administration.

Using the proposed model, individual parameters for FIX kinetics can be predicted based on only few blood samples e.g. drawn at 0, 0.5 and 48 hours after OCTAFIX administration, while flexibility is still allowed to the physician in choosing sampling intervals adapted to routine constraints. The prophylactic dosing regimen to be administered can then be calculated (assuming dose-linearity) and adapted to each patient, depending on the threshold above which FIX level should be maintained (as a function of patient's lifestyle), and its individual parameters. This approach will certainly help the management of an individualized prophylactic strategy in a routine manner.

II-41: *Andrea Henrich* Mixed effects modeling of concentration-QT relationships: first experiences with the new white paper

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Objectives: The ICH guidance documents on the analysis of drug effects on QT interval length [1, 2] were recently enhanced by a white paper with FDA scientists among its authors [3]. The technical paper defines standard analyses to evaluate QT effects at an appreciated level of detail. This work presents first experiences with this particular approach and highlights aspects that require further discussion.

Methods: A single-ascending dose study in healthy subjects provided concentration and ECG data of 6 dose groups with 8 subjects each (6 on active treatment, 2 on placebo). The compound, ACT-246475, an antiplatelet agent, was administered at doses from 1 to 32 mg [4].

Linear mixed effects (LME) modeling was employed to evaluate the effect of ACT-246475 on QT interval length change from baseline (DQTcF) [3, 5]. Estimation of intercept and slope included covariates on the intercept: treatment (active/placebo), deviation of individual baseline QTcF from average baseline QTcF (DBL), and time (categorical).

For placebo-corrected change from baseline QTcF (DDQTcF) mean and 90% confidence interval (CI), a QT effect is indicated if the upper bound of the 90% CI exceeds the regulatory threshold of 10 ms. The mean concentration-DDQTcF effect in the closed-form solution was calculated as DQTcF difference between active and placebo [3, eq. 2-5].

Robustness of results was assessed by varying concentration scale (linear vs logarithmic), analysis method (LME vs ordinary-least-squares (OLS) concentration-DDQTcF regression), derivation of CI by closed-form solution vs bootstrapping (BS). Data set programming, visualization, and modeling were performed using R and packages lme4 and ggplot2.

Results: Using concentration on a linear scale compared to logarithmic scale made a large difference. The linear scale is recommended in [3] due to undefined logarithmic values of 0 concentration (with placebo). However, on a linear scale, extreme values have a higher leverage towards the results. These few extreme observations cause the CI for the mean to be very wide. Therefore, the upper limit of the two-sided 90% CI is more likely to exceed the threshold of 10 ms, leading to a positive finding, i.e., a QT effect.

In the present case study, the linear concentration scale caused the CI to exceed the threshold of 10 ms at a substantially lower concentration (663 vs 1456 ng/mL). However, the CI of the mean included most data in the high concentration range, an implausible result since a CI can reasonably be expected to be substantially smaller than a 90% coverage interval.

Using a logarithmic scale and setting concentrations below the lower limit of quantification (LLOQ) to the LLOQ seems a reasonable choice. Setting them to smaller values can substantially influence the results, making these arbitrary to some extent.

Even though not recommended [3], rescaling of concentration was necessary to obtain model fits. Not normalizing resulted in failed convergence (lmer in R, package lme4).

OLS regression resulted in a significantly lower slope estimate (10.7 ms*mL/ng) compared to the pre-specified linear mixed-effects model (45.0 ms*mL/ng). These differences might arise from the DBL covariate in the pre-specified model.

While the CI, the key statistic in QT assessment, can be derived in closed form for the standard model, it must be derived by other means (e.g., BS) if covariates are included. This case study showed that BS CIs for concentration on the linear scale without covariates require a very large number of BS samples (10,000 or more) to be close to the closed-form solution (mean of 3.039 ms at 1305 ng/mL with closed-form solution and 3.3616 and 3.126 ms with 1000 and 10000 BS samples, respectively). This finding reflects the sensitivity of the results towards extreme values, i.e., whether or not a BS sample includes extreme values.

The exact distribution of DDQTcF follows a t-distribution. Defining the degrees of freedom is not straightforward in a mixed-effects model and [3] do not provide guidance here. We suggest that a normal distribution serves sufficiently well as approximation.

Conclusion: Even though the white paper [3] is specific in modeling details, some points of discussion remain. This case study suggests remedies and identifies a few areas for further investigation. Using a logarithmic scale for concentration data seems preferable for numerical robustness of results. For linear scales, normalization is indicated to achieve robust results.

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II-42: *Eef Hoeben* Modelling the Transfer of Sildenafil Across the Placenta with Data of an Ex-Vivo Human Placenta Perfusion Experiment

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Objectives: Sildenafil (SIL) is a selective phosphodiesterase 5 (PDE5) inhibitor. It is currently being administered to pregnant patients with pulmonary hypertension and is under evaluation as a treatment for several pregnancy complications, such as pre-eclampsia and intrauterine growth restriction. The trans-placental passage of SIL was studied in an *ex-vivo* human placenta perfusion experiment[1]. The objective of this analysis was to develop a model describing the *ex-vivo* transfer of SIL through the human placenta and to estimate the trans-placental transfer parameters (*i.e.* diffusion (CL_{cot}), placental elimination (k_{PE}) and placental partition coefficient (Kp_{pl})) of SIL from this *ex-vivo* human placenta perfusion experiment.

Methods: Six placentas were collected after term delivery from healthy volunteers, cannulated and dually perfused. Antipyrine (AP), a small non-protein bound molecule that passes the placental barrier by passive diffusion, was used as internal control. SIL and AP were added to the maternal circulation at 50 ng/mL (*i.e.* therapeutic concentration (TC); N=3) and 500 ng/mL (*i.e.* maximum tolerated concentration (MC); N=3) for SIL and at 100 mg/mL (N=6) for AP. Samples were collected from both fetal and maternal reservoir at different time points and were analyzed for SIL, its desmethyl metabolite (DM)-SIL and AP by validated LC-MSMS or -UV methods. Transfer of SIL and AP across the placenta was modelled as a cotyledon split into maternal (M) and fetal (F) compartments[2]. Data were analyzed by a non-linear mixed effects modeling approach, using NONMEM software[3]. Inter-individual variability (IIV) was evaluated using an exponential error model and residual error (RE) was described using a proportional model. The FOCE method with interaction was used for estimation of model parameters, *i.e.* $CL_{cot,}$ k_{PE} and Kp_{pl}, IIV and RE.

Results: SIL crossed the placenta at both (TC and MC) concentrations. Both maternal and fetal levels reached a plateau at 90-120 min. The FM ratios at equilibrium (150 min) were 0.83 (0.71–1.00) for TC and 0.93 (0.70-1.04) for MC. DM-SIL was not detected in any sample, suggesting negligible placental CYP3A-mediated metabolism. A 4-compartment transport model provided an adequate description of the observed *ex-vivo* data of SIL and AP in the fetal and maternal reservoir. The trans-placental transfer parameters of SIL and AP were estimated with acceptable precision. There was considerable IIV on the trans-placental parameters, especially on CL_{cot}, which might be explained by the possible contribution of other factors like drug transporters, metabolism (other than CYP3A-mediated) and/or protein binding. The estimated k_{PE} was small and may represent leakage and/or metabolism via other pathway(s).

Conclusion: SIL crosses the term placenta *ex-vivo*. The trans-placental transfer parameters could be estimated from the *ex-vivo* human placenta perfusion experiment using the developed model. The estimated values of these parameters will be implemented in a pregnant-physiologically based pharmacokinetic (p-PBPK) model in order to be able to predict the PK profiles of SIL in the fetus.

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II-43: *Nick Holford* Using Biomarkers to Predict the Target Dose of Warfarin and Linezolid

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Objective: Warfarin is widely used as a treatment of venous thromboembolism and its capability to reduce the hazard of thromboembolic events has been unequivocally demonstrated. Variability between individuals, as well as a narrow therapeutic range are barriers to safe and effective warfarin therapy. Inadequate dose individualization contributes to under-utilization, 18-55% of patients who would benefit from warfarin do not receive it, and the amount of time spent within the therapeutic range is sub-optimal for many that do receive warfarin. A theory-based mechanistic model was developed to describe the pharmacokinetics using S- and R- warfarin and pharmacodynamics using the International Normalized Ratio (INR) [1].

Linezolid has strong antibacterial activity against aerobic Gram-positive cocci (GCP), methicillin-resistant coagulase-negative staphylococci, vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus (MRSA). Thrombocytopenia and anemia are among the most important adverse effects of linezolid treatment. Linezolid-induced thrombocytopenia and anemia incidence varies considerably. Thrombocytopenia has been observed in about 10% of linezolid treated patients. Patients requiring treatment with linezolid frequently have impaired renal function and linezolid is extensively excreted by the kidneys. A pharmacokinetic and pharmacodynamic model for linezolid has been developed to predict the influence of renal function on linezolid concentration and concentration linked to the time course of development and recovery of thrombocytopenia [2].

Bayesian dose individualization methods, available at https://www.nextdose.org, have been developed for warfarin based on the INR as a biomarker and for linezolid based on total concentration (CT) and/or platelet count (PLT) as a biomarker. The objective is to use simulation and estimation techniques to evaluate the predictive performance and potential clinical utility of mechanistic models of biomarkers for dose individualization.

Methods: A simulation-estimation procedure implemented in NONMEM 7.4.1 was used to individualize doses in 1000 simulated patients. For warfarin the initial dose was 6 mg on day 1 and 3 mg on days 2 and 3 and individual doses re-estimated after each INR measurement taken 12 h after the daily dose on days 3, 7, 10, 14, 21, 28, 35, 42, 49, and 56. An external data set of patient dose and INR was used to evaluate the warfarin model [3]. For linezolid the initial dose was 600 mg every 12 h on day 1 and individual doses re-estimated after either each CT or PLT measurement taken 6 h after the first daily dose on days 1 to 14. Predictive performance was quantified using bias (mean error, ME) and imprecision (root mean square error, RMSE).

Results: Simulated predictions of the warfarin target dose were initially biased (ME: -0.56 mg/day; 95% CI: -0.59, -0.52 mg/day) and imprecise (RMSE: 2.1 mg/day). This diminished following INR measurements and dose adjustments. After six INR measurements and dose updates over 28 days, predictions were both unbiased (ME: -0.06 mg/day; 95% CI: -0.18, 0.07 mg/day) and more precise (RMSE: 0.66 mg/day. External evaluation of warfarin was unbiased (ME 0.14 mg/d; 95% CI: -0.91, 1.49 mg/day) with RMSE (0.67 mg/d) over the actual dose range of 0.75-11 mg/day.

Simulated predictions of the linezolid target dose using CT were initially biased (ME: -34 mg/day; 95% CI: -41, -26 mg/day) and imprecise (RMSE: 245 mg/day). After 4 daily CT measurements and dose updates, predictions were both unbiased (ME: -4.5 mg/day; 95% CI: -19, 10 mg/day) and more precise (RMSE: 146 mg/day). In contrast, using PLT alone did not improve the ME or RMSE after 14 days of measurements.

Conclusion: Warfarin dose individualization using INR and a theory based model is unbiased and precise as shown by simulation and external evaluation.
Linezolid dose individualization is not practical using platelet count alone. Dose individualization of linezolid should be based on measurement of linezolid concentration to improve antibacterial response and prevent the development of thrombocytopenia.

Biomarker based dose individualization should be evaluated on a case by case basis. This analysis confirmed the value of using INR as a biomarker for warfarin dose but platelet count alone is not adequate for linezolid dosing.

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II-44: *Richard Hooijmaijers* ShinyMixR: A project-centric R/Shiny run management tool for nlmixr

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Objectives: The combination of open-source packages nlmixr and RxODE, available on CRAN [1, 2] and actively developed on GitHub (http://github.com/nlmixrdevelopment/nlmixr) [1, 2], provides a non-linear mixed effects system to perform population-type pharmacokinetic and pharmacodynamic analyses and simulations [3] in R [4]. The ability to perform population modeling in R provides an opportunity to work via a single unified workflow for data management, data exploration, data analysis and report writing. The aim of this current work was to develop a user-friendly tool for nlmixr based on Shiny, which would facilitate a workflow around an nlmixr project. Ultimately, this should allow for: 1) dynamic and interactive model development, 2) quick and efficient communication of population PK-PD models, 3) rapid demonstration of simulation results from PK and PK-PD modelling (also see RxODE Shiny), and 4) reporting of modelling results [5].

Methods: ShinyMixR [6]is set up as an open source nlmixr project management tool written completely in R, and deployed as a set of R functions. The ShinyMixR system is built around a project-centric structure and provides an interface to nlmixr from both the R command line (R, related GUIs and RStudio [7]) as well as a user-friendly Shiny dashboard application [8]. The 'shinydashboard' package [9] provides a layer on top of Shiny to produce an easy-to-use dashboard which can be used for controlling and tracking runs with an nlmixr project, and was the basis for setting up the modular interface. Most of the functions underlying the interface are written such that these can be called independently from the R command line, and also work in combination with the graphical interface and vice versa.

Results: Using the ShinyMixR package, the user can specify and control an nlmixr project workflow entirely in R. Within a project folder, a structure can be created to include separate folders for models, data and runs. Functionality is available to edit and run model code, summarize and compare model outputs in a tabular fashion, and view model development using a tree paradigm. Inputs, outputs and metadata are stored in relation to the model code within the project structure (a discrete R object) to ensure traceability. The results can be visualized by using modifications of existing packages (such as xpose.nlmixr [10]), user-written functions and packages, or pre-existing plotting functionality included in the ShinyMixR package. Results can be reported using the R3port package in pdf and html format [5]. In this project-oriented structure, the command line and dashboard can be used independently and/or interdependently. As such, projects are set up to be user-centric, instead of interface-dependent.

Conclusions: The ShinyMixR package provides a means to build a project-centric workflow around nlmixr from the R command line and from a streamlined Shiny application. This project tool was developed to enhance the usability and attractiveness of nlmixr, facilitating dynamic and interactive use in real-time for rapid model development.

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II-45: *Andrew Hooker* Computation of the geometric mean and variance of the AUC using polynomial chaos

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Objectives: In many applications, a drugs pharmacokinetics (PK) can be expressed in terms of a system of ordinary differential equations (ODEs) with random parameters. One of the important PK parameters is the Area Under the Curve (AUC) which is obtained as a definite integral of a concentration function over time interval. Usually, concentration is measured at several time points, and the AUC is approximated by some approximation formula (e.g. trapezoidal rule). This result may be inaccurate, for example, due to a small number of time points taken into the approximation. Another approach is to include AUC into the system of ODEs as one of the unknown functions. One advantage of such an approach is that the (partial) AUC can be evaluated from the integration start time to any later time point. In the case of linear models, an analytical solution can be obtained for the AUC at infinity, otherwise, an appropriate numerical technique must be applied. In this work, we compare two methods of calculating the mean and the variance of the population model-based AUC. One approach is the most common Markov Chain Monte Carlo (MCMC), and another is a Polynomial Chaos (PC) method [1] which is based on a polynomial expansion of a function with respect to an appropriate system of orthogonal polynomials. There are two issues connected with MCMC: accuracy and computational time. If the sample size from parameter space is small, then there is a loss of accuracy. Otherwise, if the sample size is large then the result becomes more accurate, but the process of computation is time-consuming. The PC approach does not require any sampling techniques and does not contain any stochastic component. This allows computations to achieve similar or better accuracy in relatively less time compared to MCMC.

Methods: We consider a one-compartment model with linear oral absorption, which is represented as a system of two ODEs with three parameters (*Ka*, *CL*, *V*). *AUC(t)* is also included in the system as an unknown function: d*AUC(t)*/d*t* = *C(t)*, where *C(t)* is a concentration function. Population parameters are assumed to be known, individual parameters are assumed to be log-normally distributed. In this model, no correlations between random effects are assumed. In odder to calculate partial AUCs with the MCMC approach we sample from the individual parameter distribution, compute the AUC by solving the system of ODEs from the start of integration to each sample time point, then repeat the process many times. Finally, the mean and the variance are calculated. With the PC approach, all the unknown functions in the system are replaced with their PC expansions. After substituting these expansions into the ODEs, the initial system of ODEs with random parameters is transformed to a system of ODEs with fixed parameters which has to be solved only once. In this new system, unknown functions are the coefficients of the polynomial expansions, and the mean and the variance of the AUC are expressed in terms of these coefficients. To explore how these two approaches work the Python package **chaospy** [2] has been used as well as the R package **reticulate** for making the methods work in the R environment. Currently, the **chaospy** package only allows log-normally distributed individual parameters and non-correlated random effects. But, from a mathematical perspective, there are no limitations to extend the PC approach to more general cases.

Results: Numerical results show that the PC approach is more robust and is much faster than classical MCMC. PC has the same accuracy when the highest degree in the polynomial expansion is larger than or equals to two, while the MCMC method may have large fluctuations in accuracy depending on sample size.

Computational time for PC with a degree of expansion equal to three is twenty five times faster than MCMC with the same accuracy.

Conclusions: The PC approach can improve efficiency of AUC estimation. It requires less time to achieve the same accuracy as MCMC methods.

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II-46: *Joy Hsu* Population Pharmacokinetic and Exposure-Efficacy/Safety Analyses for the Confirmation of Alectinib 600 mg BID Dose Regimen in the Global ALK Inhibitor-Naïve Population

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Introduction: Alectinib is a tyrosine kinase inhibitor that targets Anaplastic Lymphoma Kinase (ALK) and REarranged during Transfection (RET), thereby inhibiting intracellular signaling pathways involved in tumor cell proliferation and survival. It is a potent and selective CNS-active ALK inhibitor in oral formulation. Alectinib was first approved in Japan in 2014 at 300 mg BID dose for treatment of ALK-positive, unresectable, recurrent or advanced non-small cell lung cancer (NSCLC) for crizotinib-naïve patients (i.e. first-line therapy). In 2015, the U.S. Food and Drug Administration granted approval for the 600 mg BID dose regimen for ALK-positive metastatic NSCLC in patients who had progressed on or were intolerant to crizotinib (i.e. second-line therapy).

Objectives: To confirm the appropriateness of alectinib 600mg BID dose regimen as a first-line therapy for the global patient population by applying knowledge from prior pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses on alectinib second-line therapy data to alectinib first-line therapy data collected in a global Phase 3 study ALEX following 600 mg BID regimen and in a Japanese Phase 3 study J-ALEX (conducted by Chugai Pharmaceuticals Co. Ltd.) following 300 mg BID regimen.

Methods: The PK of alectinib and its major active metabolite M4 were characterized previously using population PK models developed on Alectinib second-line therapy data [1]. A Bayesian feedback analysis was conducted by using those PK models to the PK data collected in ALEX (randomized, open-label study with PK data from 143 patients treated with 600 mg BID alectinib and 151 patients treated with crizotinib) and PK data collected in J-ALEX (randomized, open-label study with PK data from 96 patients treated with 300 mg BID alectinib and 104 patients treated with crizotinib). A total of 1518 alectinib and 1516 M4 plasma concentrations were analyzed.

Effects of exposure on main efficacy measures systemic best overall response (BOR), CNS BOR, progression free survival (PFS), and time to CNS progression were evaluated graphically for ALEX. A Cox proportional-hazards (CPH) analysis was conducted to investigate the relationship between exposure and PFS (RECIST 1.1), utilizing data from ALEX and J-ALEX. Potential influence of additional factors such as baseline disease status covariates (e.g., tumor size, Eastern Cooperative Oncology Group score, CNS-metastases status, prior chemotherapy) and demographic covariates (e.g., body weight, age, gender, race, ethnicity, smoking status) were investigated. To investigate the exposure-safety relationship between exposure and safety parameters serious adverse event (SAE) and any adverse events (AE) Grade 3 or above, logistic regressions were conducted.

Results: Bayesian feedback analysis showed that the PK characteristics of alectinib and M4 in patients who were ALK inhibitor-naïve are consistent with that in patients previously treated with crizotinib. Body weight was confirmed to be the only significant covariate for the PK of alectinib and M4, as identified in the previous population PK analyses [1]. Administration of 600 mg BID regimen ensures that all patients across

the entire body weight range in global population would achieve steady-state exposure which is not inferior to that achieved following 300 mg BID regimen in J-ALEX.

Results of the graphical exposure-efficacy showed that variability in alectinib exposure at 600 mg BID does not explain the variability in efficacy. Across the dose range of 300-600 mg BID for alectinib, results of the CPH analysis indicated that greater PFS benefits were found for patients treated with alectinib compared to crizotinib, with the most PFS benefit identified for patients in the high exposure category. The PFS benefit was found to decrease with increasing baseline tumor size. Simulations using the CPH model for PFS showed that the 600 mg BID dose regimen would provide greater PFS benefit over crizotinib compared to the 300 mg BID dose regimen. No significant exposure-safety relationship was identified following 600 mg BID in ALEX.

Conclusions: Results of these analyses demonstrated that alectinib 600mg BID is the appropriate dose regimen for all the ALK-inhibitor naïve ALK-positive NSCLC global patient population.

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II-47: *Wilhelm Huisinga* Cell-level based tumor cPBPK model to study mAb distribution within solid tumors and implications for efficacious treatment

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Objectives:

Heterogeneous distribution of antibodies within tumor tissue, often discussed in the context of the `binding site barrier', is still a current topic of debate, in particular for antibody-drug conjugates (ADCs)[1]. Furthermore, for monoclonal antibodies (mAbs) competing with a natural ligand for receptor binding, receptor inhibition is also an important measure for efficacy. The objective was to comprehensively investigate mAb distribution within tumor tissue and its implications on therapeutic efficacy based on a mechanistic modelling framework that allows to study in detail receptor saturation and receptor inhibition.

Methods:

Model development was based on a consensus PBPK (cPBPK) model for mAbs [2] that incorporates total plasma in addition to various tissues with an extravasation-rate limited tissue distribution model for organs except tumor. The cPBPK model is fully specified by readily available physiological and drug-specific parameters for various species, validated ABC values [3] and a-priori median unspecific clearance with one equation per tissue. The model thus allows to a-priori predict target independent mAb disposition processes as well as mAb disposition in concentration ranges, for which the linear unspecific clearance dominates target-mediated clearance processes. This is often the case for mAb therapies at steady state. The cPBPK model has successfully been validated against preclinical and clinical data. For the present study, the cPBPK model was extended by a detailed tumor distribution model (Krogh cylinder geometry). The Krogh cylinder is divided into sub-compartments that represent the tumor tissue around the blood capillary. Tumor parameters were taken from literature [1] and were not fit to data. Furthermore, the tumor model integrates a single cell-level modelling approach [4,5] to account for antibody-receptor-ligand interactions as well as receptor dynamics.

Results:

The experimentally observed heterogeneous drug distribution within solid tumor tissue in xenograft mice following approved clinical dosing regimens of ADCs [1] was confirmed based on the cell-level based tumor cPBPK model and considered as a first validation of the extended approach. Extrapolation to patients, however, predicted a homogenous drug tumor distribution following clinical dosing regimens of ADCs. The qualitative species-differences may be related to a marked difference in tumor volume per kg body weight, which is almost 2-3 orders of magnitude larger in xenograft mice than typically in patients. As a consequence, target-mediated mAb disposition dominates linear clearance in mice, resulting in faster declining PK profiles. In humans, however, linear unspecific mAb clearance is the dominating clearance process, and its inter-individual variability has a marked influence on the duration of receptor saturation. In the context of multiple dosing and if receptor saturation is required for efficacy, this finding has important

implications (i) for the first treatment cycle and (ii) in the case of increased unspecific CL (e.g., due to immunogenicity). In addition, if the mAb is competing for receptor binding with a natural ligand we found that residual receptor activity (in contrast to receptor saturation by the mAb) may largely differ.

Conclusions:

The cell-level based tumor cPBPK offers a mechanistic framework to especially investigate the dosing regimen within the initial treatment period of ADCs targeting solid tumors and to study the impact of antibody receptor affinity as well as the tumor micro-environment (e.g., ligand concentration within tumor) on residual receptor inhibition and receptor saturation.

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II-48: *Yun Hwi-yeol* Accurate and Precise Prediction of in-vivo hepatic clearance for drug with low KM

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Objectives: The procedure for prediction of in vivo hepatic clearance using in vitro kinetic data from liver microsomes is well-established and is in wide use [1]. The approach derives from calculation of intrinsic clearance (CL_{int}) based on Michaelis-Menten (MM) kinetics, with the assumption that total enzyme concentration at the active site (E_T) was much lower than the Michaelis constant (K_M). However, in drugs with very low K_M, predicted results could be inappropriate because the above assumption failed to hold [2]. The main aim of this study is to afford a comparison of standard and new in vivo hepatic clearance methods using drugs with low K_M and suggestion of new strategies for appropriate prediction in these drugs.

Methods: Mathematical close review was performed to overcome the assumption inherent in the standard approach and new mathematical equations were investigated. To compare and evaluate the standard and new approaches, a simulation study was conducted before application with a real case. Twenty-five examples of in vitro kinetic data from human liver microsomes and real human hepatic clearances were obtained from references [1, 3-6]. Hepatic clearance(CL_h) was calculated by standard and new methods using collected in vitro data, and were subsequently compared with real in vivo data to evaluate the accuracy and precision of these methods.

Results:

An alternative model which accurately describes the drug metabolism even when $E_T << K_M$ does not hold can be derived with the simple modification of the MM model:

$$dP/dt = k_{cat}\cdot E_T\cdot S^{-}/(K_M + E_T) = CL_{int}\cdot E_T\cdot K_M\cdot S^{-}/(K_M+E_T),$$

where $S^{-} = S + C$. This model is referred as the new model in this study. This leads to the new prediction formula for the in-vivo intrinsic hepatic clearance ($CLu_{H,int}$):

$$CLu_{H,int}\ (mL\ min^{-1}) = CL_{int}\cdot E_T\cdot K_M/(K_M + E_T)\ (mL\ min^{-1}).$$

For the next steps to obtain in-vivo hepatic clearance(CLu_H) from intrinsic hepatic clearance, the well-stirred model was used for pattern description of liver disposition of drugs.

$$CLu_H = Q_H\cdot f_{ub}\cdot CLu_{H,int}/(Q_H + f_{ub}\cdot CLu_{H,int})$$

For all of the parameters, accuracy and precision parameters (average fold error (AFE) and Root Mean Squared Prediction Error (RMSE)) were consistently by over 50% using the new methods.

Conclusions: In drugs with low K_M, error could potentially be generated when predicting the hepatic clearance using in vitro kinetic data. Normalizing CL_{int} by enzyme total concentration was able to overcome this issue for drugs of this kind and the use of these equations is recommended in this situation.

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II-49: *Moustafa Ibrahim* Model-based post-processing of CWRES for assessment of prediction bias

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Background and Objectives: Conditional weighted residuals (CWRES) modelling has been proposed as easily automated diagnostic tool for model development/evaluation process, as it provides guidance for the nature and magnitude of potential model misspecification/improvements. [1] In this work, a method based on CWRES modelling was developed to assess prediction bias by back-extrapolating a CWRES-based bias using the first order conditional estimation (FOCE) approximation. We illustrate this method by assessing prediction bias in two integrated models for glucose homeostasis, the integrated glucose insulin (IGI) model and the integrated minimal model (IMM) [2,3,4]. Both models consist of glucose and insulin sub-models with interconnecting control mechanisms, and were proposed to describe simultaneously the glucose-insulin regulation system following intravenous glucose tolerance test (IVGTT) in healthy subjects.

Methods: One dataset was simulated from each model according to a standard IVGTT protocol, then analyzed by the two models and visual predictive checks VPCs were performed to investigate the goodness of each fit. CWRES outputted from each model fitting was separated based on the two dependent variables (DVs) glucose and insulin, where after CWRES for each DV was modelled by a base model to estimate CWRES distribution's mean and variance. The base model was then extended to estimate different means for ten bins of the independent variable (IDV) at cutoffs points of the IDV dictated by data-density, this could capture systematic trends in CWRES as well as the magnitude of structural model misspecifications in terms of difference in objective function values ΔOFV_{Bias} (when significant) between this model and CWRES base model. The estimates of the bin-specific means were used to calculate the corresponding bias in conditional predictions at each bin of the IDV by the inversion of FOCE-based CWRES equation. TIME, glucose PRED, and insulin PRED were the investigated IDV, and a random binning technique was implemented to avoid binning introduced bias. [5]

Results: When either of the two data sets were analyzed with the IGI model, or data simulated by the IMM was analyzed by the IMM, ΔOFV_{Bias} was insignificant for both DVs glucose and insulin. When data simulated by the IGI was analyzed with the IMM, ΔOFV_{Bias} was significant for glucose, but not for insulin. Over prediction bias in glucose sub-model was found at early time points (

Conclusions: New method for predication bias assessment based on CWRES was developed and successfully applied to two integrated, complex models for glucose homeostasis. The new method identified correctly the bias in glucose sub-model of the IMM, when this bias occurred, and calculated the magnitude of the resulting bias. This new method is fast and easily automated diagnostic tool for model development process, and it is already implemented as part of the **qa** tool in PsN.

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II-50: *Ibrahim Ince* A Population Physiologically-Based Pharmacokinetic Model for prediction of pharmacokinetics of small molecule drugs in healthy Japanese adults: Bridging PBPK from Caucasian to Japanese ethnicity

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Objectives: Physiologically-based pharmacokinetic (PBPK) modeling is considered a valuable tool for predicting pharmacokinetic changes of drugs in different populations to subsequently guide *in-vivo* pharmacokinetic trials. The goal of this study is to extrapolate physiologically-based pharmacokinetic models for small molecule drugs in healthy Caucasian adults to healthy Japanese adults. Predictive performance of this bridging approach is verified by predicting the pharmacokinetics of small molecule drugs acetaminophen, ciprofloxacin, midazolam, and theophylline in healthy Japanese adults and comparing to clinically observed data.

Methods: A systematic literature search was carried out to identify and collect study data on Japanese anatomical, physiological, and functional parameters to establish a PBPK population model for healthy Japanese individuals. The database was implemented in the Open Systems Pharmacology (OSP) Suite [1]. Small molecule drugs for verification of the predictive performance of the PBPK model were selected according to the availability of published data. First, PBPK models for the small molecule drugs acetaminophen, ciprofloxacin, midazolam, and theophylline were created in Caucasian adults. Subsequently, these population PBPK models were applied to predict the PK of the four compounds in Japanese adults, where the activity and variability of relevant enzymatic processes (e.g. CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2E1, CYP3A4, SULT1A1, and UGT1A1) was implemented. Bridging the PBPK models from Caucasian to Japanese adults accounted for the differences in anthropometric, anatomical and physiological parameters (e.g. body weight, body height, organ volumes, blood flow rates and tissue composition). Prediction results were evaluated by comparison with experimentally observed literature data and with comparison of observed versus predicted PK measures.

Results: PBPK population models for healthy Japanese were established in the OSP Suite. PK for acetaminophen, ciprofloxacin, midazolam, and theophylline in Caucasian and Japanese adults was extracted from literature. First, population PBPK models in Caucasian adults including the relevant enzymatic processes were established and successfully predicted the PK of acetaminophen, ciprofloxacin, midazolam, and theophylline. Second, the PBPK models for these small molecule drugs were extrapolated and correctly predicted the PK in the Japanese adult population. As a result, for Caucasian and Japanese, more than 90% of the predicted mean plasma concentrations and PK measures for all drugs fell within the 2-fold error range of the reported values.

Conclusions: We successfully developed four Japanese population PBPK models and systematically evaluated the predictive performance of these extrapolated PBPK models from healthy Caucasian to Japanese adults using acetaminophen, ciprofloxacin, midazolam, and theophylline as exemplary small molecule drugs. Ultimately, this bridging approach could be applied to investigate *in silico* the PK of other small molecule drugs and help design clinical trials in Japanese adults.

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II-51: *Mohamed Ismail* An open source software solution for automating pharmacokinetic/pharmacodynamic model selection

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Objectives:
The current approach to population PKPD model selection is formally known as downhill search and is a local search method. Out of necessity, the approach greatly reduces the sample space of possible models by proceeding in a stepwise manner, first finding the best structural model, then searching for significant covariate relationships and statistical models. Not only is the approach inefficient, it is also not guaranteed to find the optimal solution due to interaction between model components [1]. Further, this method involves many repetitive (i.e. testing various covariate forms) and predictable processes that lend themselves to automation.

Genetic algorithms (GA) are a class of global search methods inspired by the mathematics of evolution. They can be used to find global optimal solutions for difficult problems even in the presence of non-differentiable functions, as is the case in the discrete nature of including/excluding model components in search of the best performing mixed-effects PKPD model [2, 3].

The objectives of this work were to harness the capabilities of GA for automated PKPD modeling, and create an open source software application to implement these algorithms for widespread use and continued community development.

Methods:
Software
The program is built in R [4], and includes a Shiny GUI. It has been integrated with PsN and xpose4.

The Control Stream Template
To implement the GA, the construction of the NMTRAN control stream is altered slightly to allow for programmatic editing of the text. A control stream template resembles a typical NMTRAN control stream but includes model placeholders. The placeholders are then replaced by the program to construct syntactically correct control streams.

The Chromosome
A model is represented by a "chromosome", which is made up of a collection of model characteristics, or genes.

Fitness
The fitness of a model is determined by the value of the objective function with penalty terms.

Fitness= -2LL+5×NParam+10×UnsuccessfulCovariance+20×UnsuccessfulMinimization

In this context, a smaller value indicates a more fit model.

Initializing the GA

The GA begins with randomly selecting an initial population of models. The models are run in parallel by calling PsN's execute. Upon completion, the program calculates the fitness of each model and continues to the selection phase to determine the next generation of models.

Selection
Tournament selection was implemented. It is a ranked selection method and is ideal in instances when fitness values are close in magnitude.
More fit models have a higher likelihood to proceed to be "parents" in the next generation, and can be included more than once.

Crossover
The crossover genetic operator mimics biological reproduction, swapping genes of parent models to produce new, potentially more fit models. To implement crossover, the algorithm randomly selects two points along the parent chromosomes, and swaps all genes between those points.

Number of compartments, Age on CL, Weight on V, SexM on CL, Absorption, Residual error
1, None, Linear, Additive shift, First-order, Proportional
2, Linear, Power, None, Zero-order, Proportional
^ ^
^ = Crossover points

Children models:
1, None, **Power, None,** First-order, Proportional
2, Linear, Linear, Additive shift, **Zero-order, Proportional**

Mutation
The mutation operator is implemented on the child models produced by crossover. Each gene of each model has a small probability to be mutated. Mutation randomly changes the phenotype of a gene. Mutation promotes diversity in models and introduces new genetic material.

Results:
The application performs automated model selection of the globally optimal population PKPD model. It not only returns a single best model, but ranks all models that were run in a tabular interface, allowing the modeler to select from among the best models based on diagnostic plots or other criteria.

In addition to the GA implementation, the application serves as a convenient workbench for NONMEM. Features include

- Organizes and displays models in tabular format, allowing the user to sort, filter, edit, create, and delete models
- Displays run results and parameter estimates
- Integrated with xpose4 and PsN to create diagnostic plots and run PsN scripts

Conclusions:
An automated solution for population PK/PD modeling will allow modelers to focus on hypothesis generation and model evaluation rather than text processing and model execution.

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II-52: *Julie Janssen* Semi-physiological Pharmacokinetics of Bortezomib in Pediatric Patients with Acute Lymphoblastic Leukemia

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Objectives: Bortezomib is a proteasome inhibitor targeting the 20S proteasome used in the treatment of adult multiple myeloma, and is currently under investigation for treatment of children with relapsed acute lymphoblastic leukemia (ALL). The pharmacokinetic (PK) profile of bortezomib is nonlinear and is characterized by a large volume of distribution and a rapid decline in plasma concentrations within the first hour after intravenous (iv) administration. Furthermore, a marked increase in exposure was observed in the second week of treatment (1, 2, 3). This has previously been explained by extensive binding of bortezomib to proteasomes in erythrocytes and peripheral tissue (4). The primary aim of the current study was to develop a PK model for bortezomib in order to evaluate the currently used dosing regimen in pediatric patients. The secondary aim was to understand the time-dependent change in bortezomib exposure.

Methods: 323 samples of 28 patients (1.0 – 17.5 years old) were available from the ITCC 021/I-BFM-SG-study (EudraCT number: 2009-014037-25). Patients were treated with an iv bortezomib dose of 1.3 mg/m^2 in a twice-weekly schedule (administrations on day 1, 4, 8 and 11). PK samples in plasma and cerebrospinal fluid (CSF) were collected after the bortezomib administrations on day 1 and 11 at 7 time points (pre-dose and 15 minutes, 3, 8, 24, 48, 72 hours after dose). A semi-physiological PK model for bortezomib was developed incorporating saturable binding of bortezomib. The Langmuir model was used to describe the non-linear binding of bortezomib in the central compartment. Allometric scaling was applied to all structural model parameters. Correlations between PK parameter estimates and age were investigated to identify a possible maturation effect. Visual assessment of the model was applied by goodness-of-fit plots and prediction-corrected visual predictive check (pcVPC). Uncertainty on model parameters were calculated using the Sampling Importance Resampling (SIR) procedure.

Results: Bortezomib concentrations in CSF were undetectable in the majority of the samples (83.5%). The plasma data was best described by a two-compartment model with large volumes of distribution (V1 = 69.7 L (97.5% confidence interval (CI) 46.0 – 105.0 L) and V2 = 656 L (97.5% CI 417 - 1019 L)) and systemic clearance of 5.95 L/h (97.5% CI 3.56 – 9.24 L/h). Increased concentrations were observed on day 11 compared to day 1. Non-linear binding in the central compartment was best described by a saturable Langmuir model. The population value of the maximal specific binding capacity (B_{max}) was 60.7 ng/mL (97.5% CI 35.1 - 105 ng/mL) with 52.1% (97.5% CI 39.8 – 69.3%) inter-individual variability. The corresponding equilibrium dissociation constant (K_D) was 60.2 ng/mL (97.5% CI 32.5 - 110 ng/mL). Maturation effect and other covariate effects could not be identified. The goodness-of-fit plots and pcVPC indicated that the developed model adequately captured the PK and variability of the data.

Conclusions: The semi-physiological model adequately described the nonlinear PK of bortezomib in plasma. Saturable binding, probably to erythrocytes, provides an explanation for the increased exposure in the second week of treatment. Additionally, the final model parameters were in agreement with reported adult values.

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II-53: *David Janzén* Estimating absolute bioavailability in population models despite lacking IV data

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Introduction: Mathematical modelling is widely applied as a tool for gaining insights into a biological system by means of formalizing the underlying biological mechanisms into a set of ordinary differential equations (ODE). These equations contains parameters of which some are known, whilst the remaining parameters are estimated using data from experiments. A subset of the estimated parameters are often subject to biological interpretations, e.g., potency or bioavailability of a drug.

Parameter identifiability, of which there are two types, is in this context important as it concerns how well-determined the parameters are. Practical identifiability is the study of how lack of information and noise levels in the measurements translates into the uncertainty in the parameters estimates. Structural identifiability however, is the study of whether there exist a unique, or otherwise, solution to the inverse problem under the condition of continuous noise-free data given a particular set of input and output functions to a model [1]. Structural identifiability is therefore a prerequisite for successful parameter estimation and subsequent biological interpretations. This is because structurally unidentifiable (SU) parameters can have any numerical value whilst the observed model output remains the same. Furthermore, while a model with a unique solution to the inverse problem is called a structurally globally identifiable model (SGI), a model with more than one solution, but a finite number of solutions, is called structurally locally identifiable (SLI). The one-compartment absorption model is an example of a SLI model, but is in a drug discovery context more commonly known as a flip-flop model.

Structural identifiability for models defined by ODE's has extensively been studied and several methods have been developed, see for instance [4,5]. However, up until recently no theoretical framework or analytical methods for studying structural identifiability in population models has existed. In [2,3] methods for analyzing both linear and nonlinear models in a population setting are described. Results from applying these methods so far indicates that structural identifiability results in a deterministic setting does not necessarily translate to the population setting. In this work we have studied this by focusing particularly on the one-compartment absorption model in a population setting.

Objectives:

- Show analytically that identifiability of bioavailability is dependent on the postulated distribution model in the one-compartment absorption model
- Evaluate the error of the estimated bioavailability when postulating the wrong distribution model
- Study numerically the required numbers of samples and subjects necessary to estimate the bioavailability with a logit-normal distribution, while clearance, volume and absorption rate are log-normally distributed, when IV data is lacking

Methods: Recently published analytical methods [2,3] applicably to population models were here applied to the one-compartment absorption model. In summary, by generating the *exhaustive summary* [6] for the deterministic version of the population model and studying its distribution the identifiability of the population model can be determined analytically. For the numerical approach, data was generated with the one-compartment absorption model using known values of the population parameters and the distribution

parameters. The parameters where then re-estimated using different numbers of samples and subjects with the correct and incorrect postulated parameter distributions.

Results: The analytical result show that if a lognormal distribution of bioavailability is used the model will be unidentifiable. However, if a logit-normal distribution is postulated for the bioavailability then the model is (at least) SLI. The numerical part of this study confirms that while the true bioavailability can indeed be estimated with a logit-normal distribution it is highly affected by the quality of the data. In addition, if a lognormal distribution is used but the true distribution is logit-normal, the error in the estimate of the bioavailability will depend on how similar the logit-normal distribution is to a lognormal distribution.

Conclusion: The presented results concludes that the population bioavailability, but not individual estimates, can be estimated despite lacking IV data if the distribution is postulated to have a logit-normal distribution.

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II-54: *Petra Jauslin* Population Pharmacokinetic Analysis of Tildrakizumab, an Anti-IL-23 Antibody, in Healthy Volunteers and Subjects with Psoriasis

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Objectives: Tildrakizumab is an anti-IL-23p19 monoclonal antibody (mAb) in development for the treatment of chronic plaque psoriasis. The objectives of this analysis were to characterize the population pharmacokinetics of tildrakizumab and to identify intrinsic and extrinsic factors influencing its exposure in healthy volunteers and subjects with psoriasis across all clinical development phases.

Methods: Subcutaneous (SC) administration arms of six Phase 1, 2b and 3 trials were included in the analysis data set, containing 2098 individuals and 13967 observation records in total. Model development was performed in NONMEM 7.3 [1] / PsN 4.2.0 [2]. A formal covariate analysis was conducted; covariates were evaluated in a stepwise procedure with forward addition ($\alpha = 0.01$) followed by backward elimination ($\alpha = 0.001$). Covariates of interest included body weight, gender, age, race, ethnicity, Japanese origin, patient status, serum albumin, creatinine clearance, prior treatment with a biological agent and formulation type. The model was validated by a prediction-corrected visual predictive check [3] and a bootstrap analysis [4]. The impact of covariates and need for dose-adjustment was assessed by conducting univariate and multivariate covariate simulations.

Results: The base model was a 1-compartment model (parameterized in terms of clearance (CL) and volume of distribution (V)) with first order absorption and elimination, and inter-individual variability on CL, V and absorption rate constant (KA). The residual error structure was combined proportional and additive. Relative bioavailability was significantly higher in healthy subjects than in psoriatic subjects. Including this covariate in the base model was necessary to obtain an acceptable fit. The difference between healthy subjects and psoriatic subjects was partially explained by body weight. Hence, body weight was included as structural covariate on apparent total clearance (CL/F) and apparent volume of distribution (V/F) in the base model as well.

Though most covariates (body weight, gender, age, race, ethnicity, patient status, serum albumin, creatinine clearance and formulation) turned out to have a statistically significant effect on one or several model parameters, these covariate effects – with the exception body weight and patient status (healthy versus psoriasis patient) - were found to be small to modest. Inclusion of additional covariates on top of body weight and patient status (both part of the base model) had little effect on inter-individual variability (IIV CL decreased by 3%, other IIVs unchanged) and no effect on residual error estimates.

The final population PK model indicated that psoriatic subjects were characterized by a geometric mean (%CV) clearance of tildrakizumab of 0.32 L/day (38%), volume of distribution of 10.8 L (24%), absorption and elimination half-life (t½) of 1.5 days (18%) and 23.4 days (23%), respectively, and an absorption lag time of 0.05 days (1.2 hours).

Univariate and multivariate simulations showed that the effects of all identified covariates on tildrakizumab steady-state AUC and Cmax were within the established clinical comparability bounds that would be expected to result in no important change in tildrakizumab efficacy or safety.

Conclusions: All covariate effects except body weight and patient status were found to be small to modest. Patient status is not relevant in clinical practice, as the drug will not be administered to healthy subjects. Simulations showed that the body weight effect was still contained within clinical comparability bounds. Based on PK data only, there is no need for dosage adjustment for the evaluated intrinsic and extrinsic factors. Nonetheless, body weight was influential and was subsequently evaluated in a PKPD analysis.

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II-55: *Garrit Jentsch* A repeated time-to-event model is superior to a count regression analysis in linking FVIII activity to bleeding events in prophylactically treated patients with severe haemophilia A

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Objectives: The objective of this analysis was to investigate whether a PK/PD relationship could be established between the activity-time profile of factor VIII (FVIII) and the occurrence of (repeated) bleeding events in patients prophylactically treated with BAY 94-9027. Two modelling approaches were compared for this task. In particular, it was evaluated whether a repeated time to event (RTTE) analysis and a standard regression analysis relating the average time without optimal FVIII protection (independent variable) to the annual number of bleeds (dependent variable), would both identify a significant exposure response (ER) relationship. Additionally, a covariate analysis was conducted to evaluate whether sources of inter-individual variability (IIV) in the bleeding pattern could be identified.

Methods: Data from two phase 2/3 clinical trials were analyzed, in which patients with severe hemophilia A were prophylactically treated with BAY 94-9027, a PEGylated recombinant FVIII product currently under clinical development. Individual FVIII activity-time profiles were predicted using the individual post-hoc estimates from a previously developed population PK model. For the standard ER analysis, these profiles were used to calculate the average weekly times that the patients spent below a certain FVIII threshold level, which varied between 1 and 20 IU/dL. These times without optimal protection were used as independent variable in a count regression analysis [1]. Moreover, the individual activity time profiles were employed in the second part of the analysis in which an RTTE model using non-linear mixed-effects modelling [2] was developed. The RTTE model was qualified using visual predictive checks (VPCs), which compared the observation-based Kaplan-Meier curves of the first six bleeding events to the respective model-predicted survival functions. Moreover, covariate effects were visualized by generating VPCs stratified according to the identified covariate relationships.

Results: In the standard ER approach, a statistically significant relationship (p<0.01) could not be identified between the time spent without optimal FVIII protection and the annual number of bleeds. In the second part of the analysis, an RTTE model with log-normally distributed bleeding intervals was selected as a base model. An Emax model was used to describe the effect of the FVIII activity on the hazard. Accounting for the individual FVIII activity-time profiles in the hazard function was highly significant (p<0.0001). Furthermore, the number of reported bleeds in the past year prior to study begin (NSB) was identified as a significant covariate on the parameter mu of the log-normal hazard function. A power model with an exponent of -0.0169 was found to describe this relationship such that an increase in NSB leads to a decrease in the length of the bleeding intervals.

Conclusions: A standard regression approach, which neglects both the times of the bleeding events and the dynamics of the FVIII kinetics, failed to establish a significant ER relationship, whereas an RTTE model successfully established a relationship between the individual FVIII activity-time profiles and the occurrence of bleeding events. The medical history of the patients was identified as a significant source of IIV. Moreover, the FVIII kinetics of BAY 94-9027 has a quantitatively similar effect on the occurrence of bleeding events as the non-PEGylated FVIII BAY 81-8973 [3]. The estimated EC50 values of the two compounds were almost identical (8.15 and 9.14 IU/dL for BAY 94-9027 and 81-8973 respectively), which indicated that the

effectivity of the compounds did not change and that any differences between the two compounds are PK driven.

Moreover, it is tempting to speculate that the standard regression approach, which neglects both the exact bleeding times and the dynamics of the FVIII kinetics, failed to establish a significant ER relationship because no placebo group was included in the analysis and the studied doses were selected such that all patients benefited from treatment.

In the field of prophylactic treatment of hemophilia A patients with recombinant FVIII, this work demonstrates the superiority of an RTTE approach compared to a classical ER endpoint approach. In addition, the RTTE model can be simulated in order to evaluate clinical relevant scenarios such as the effects of different dosing schedules.

Conflict of Interest: ASo, ASh, and DG are employees of Bayer Pharma AG. GJ and JG were payed consultants for Bayer AG.

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II-57: *Martin Johnson* Artificial neural networks can facilitate the analysis and prediction of longitudinal tumour size data: an example from a non-small cell lung cancer phase III study

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Objectives:

Artificial Neural Networks (NN) are an important component of modern Machine Learning. They have been used in a wealth of applications such as recognition algorithms, Engineering, Biology or Finance. However, the use of artificial NN in pharmacometrics is limited [1, 2]. Artificial NN are powerful learning algorithms which is capable of establishing input and output relationships for complex data where these relationships might not be obvious (artificial NN do not assume any specific structural model). We examined the applicability of artificial NN to analyse tumour progression and identify associated factors using data from a non-small cell lung cancer (NSCLC) phase III study.

Methods:

Osimertinib is an approved drug for the treatment of patients with T790M mutation positive advanced NSCLC who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [3]. Data used in this analysis were collected from a phase III study (AURA3; NCT01801632; osimertinib vs chemotherapy) including patients with advanced NSCLC. Longitudinal sum of the longest diameter (SLD) collected from 257 patients (1695 SLD measurements) dosed with osimertinib were analysed. Baseline SLD, age, gender, race, metastatic status, WHO status, smoking status, information about previous therapy, lactose dehydrogenase (LDH) at baseline, albumin level (at baseline, week 6, week 12 and week 18), neutrophil to lymphocyte ratio (NLR) (at baseline, week 6, week 12 and week 18) were used as features (covariates) to predict the longitudinal changes in SLD. Time variable was included in the model as covariate. An artificial NN approach as implemented in 'nnet' R package was applied to predict the longitudinal SLD. In addition, functions from 'caret' R package were used to build the model. The available dataset (1695 observations) were randomly partitioned in 80/20 ratio as training and test dataset and artificial NN were trained using the training dataset and the model was validated using test dataset. Number of nodes (hidden units) and decay rate were tuned and root mean squared error (RMSE) used as a metric to evaluate the model. Predictor variables were then identified by order of importance. Artificial NN approaches are data driven and hence, 1000 bootstrapped datasets were used to evaluate the sensitivity of the model outcome. Artificial NN was applied on 1000 bootstrapped datasets and the top 5 predictors were identified for each dataset. Further, the predictors were selected based on the 5 most frequent predictors identified from all the bootstrapped datasets.

Results:

Following the training procedure, we obtained an artificial NN which was able to predict the SLD up to 78 weeks. The predictions from the training and test dataset were close to observation with root mean square error (RMSE) of 0.0450 and 0.0655, respectively. Based on the 1000 bootstrapped datasets, baseline SLD,

NLR at week 6 and 18, LDH at baseline, and age at baseline were identified as the 5 most influential predictors for changes in longitudinal SLD. Albumin levels and systemic drug exposure were also identified as potential predictors, but to a lesser extent. Artificial NN identified predictors could be potentially tested as covariates in a pharmacometric model describing changes in longitudinal SLD over time. Because the model was built using SLD up to 78 weeks, the outcome beyond 78 weeks may be unreliable.

Conclusions:

Our artificial NN model is able to predict the trends in SLD up to 78 weeks. Baseline SLD, NLR at weeks 6 and 18, LDH at baseline, and age at baseline were identified as the most influential predictors for changes in longitudinal SLD. We plan to further investigate the generalisation of this result by analysing larger number of clinical data via artificial NN.

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II-58: *Koen Jolling* Population pharmacokinetic modelling of CHF6001 following dry powder inhalation in healthy volunteers.

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Objectives: CHF6001 is a potent and selective phosphodiesterase-4 (PDE-4) inhibitor to treat chronic obstructive pulmonary disease (COPD) and asthma. CHF6001 is being developed for inhalation to help overcome the well-known gastrointestinal side effects associated with this therapeutic class when given orally [1]. Data from 2 phase I studies were used to evaluate the population pharmacokinetics of CHF6001 and to investigate the influence of selected covariates on CHF6001 PK parameters. While initially available in Hard Gelatine Capsules delivered by the Aerolizer® device, CHF6001 is now developed via the novel multi-dose NEXThaler inhaler®. The goal of the analysis was to simulate CHF6001 plasma profiles of relevant clinical doses to be administered via the NEXThaler® inhaler.

Methods: CHF6001 plasma concentrations (2931 samples from 100 subjects) after inhalation in healthy volunteers were obtained from 2 phase I dose escalation (SAD & MAD) studies: study FIH and study Extension. Both studies were double-blind, randomized, placebo-controlled. In the MAD part of FIH study, doses were administered once daily via the Aerolizer® inhaler, while in the Extension study administration was twice daily via the NEXThaler® inhaler. CHF6001 concentrations were modelled with non-linear mixed-effect approaches using NONMEM V7.3.0. The explored covariates were inhaler device (FORM), body weight (WT), body mass index (BMI), age and sex. Simulations were done for a total daily dose of 2400µg to compare once and twice daily dose regimens with the NEXThaler device.

Results: The final model describing CHF6001 PK was a two-compartment disposition model with 3 parallel absorption pathways (slow, intermediate and fast) and first-order elimination, similarly as the one developed by Borghardt et al. [2]. The residual error model was a combination of a proportional and an additive component for the non-transformed data. For both devices the majority of the available dose was absorbed via the slow pathway (D2, KA2). This fraction was estimated to be 62.8% and 41.3% of the bioavailable dose for NEXThaler® and Aerolizer®, respectively. The smallest available fraction, 10% for NEXThaler® and 12% for Aerolizer®, was absorbed via an early very fast pathway (D3). The remaining fraction, 27.2% for NEXThaler® and 26% for Aerolizer®, was absorbed via the early intermediate pathway (KA1). The absorption rate constant for the latter pathway (KA1) was estimated to be 39.9% higher for Aerolizer® as compared to NEXThaler®. When using the Aerolizer® device, the median C_{max} was found to be 8% higher, for a dose of 2.4 mg, as compared to the NEXThaler® device, while the AUC was found to be 20.7% lower. T_{max} with the Aerolizer® device was found to be 1 hour faster as compared to the NEXThaler® device (2 hours versus 3 hours after dose). Simulating the same total daily dose but with different regimens (i.e. QD vs. BID) via the Nexthaler® device, a similar 24h exposure was obtained, but with BID dosing resulting in 35% lower fluctuation (calculated as C_{max}-C_{min}/C_{av}) and 11% lower C_{max}.

Conclusions:

The PK of CHF6001 could be described by a two-compartment disposition model with 3 parallel absorption pathways and first-order elimination. Physiologically, being the gastrointestinal drug availability of CHF6001 very low, the 3 absorption pathways may represent 3 different compartments of the lung; a fast absorption pathway (D3) associated to the distal small airways and an intermediate (KA1) and slow pathway (D2)

associated to upper airway regions. The slow absorption (D2) could account for a long drug retention into the lung, potentially leading to tight engagement at the target receptors.

The Nexthaler® device was characterised by a higher drug availability in comparison to the Aerolizer®. In addition, simulations with the Nexthaler® device supported twice-daily administration, with lower C_{max} and lower fluctuation than once daily dosing. This could be associated to reduced risk of systemic adverse effects and better engagement at the target receptors.

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II-59: *Fredrik Jonsson* Exposure-Response Modeling of Emicizumab for the Prophylaxis of Bleeding in Hemophilia A Patients

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Objectives: Emicizumab has recently been approved in the US for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A with factor VIII (FVIII) inhibitors. Emicizumab is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX) and has co-factor activity that substitutes for activated FVIII. Therefore it is capable of promoting the activation of FX by FIXa. Emicizumab activates downstream hemostasis at the site of bleeding in hemophilia A patients who have hypofunctional levels or entirely lack FVIII [1]. Up to 30% of patients with hemophilia A develop neutralizing alloantibodies against FVIII (inhibitors). In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII.

Our main objective is to assess and quantify the relationship between exposure to emicizumab and reduction in the annualized bleeding rate (ABR) among hemophilia A patients. In addition, we want to perform simulations exploring the effect on bleeding count at different doses in order to support the intended dose regimen

Methods: Bleeding event data were pooled from 301 hemophilia A patients participating in four clinical studies [2-6], including one non-intervention study where no emicizumab was given [6]. Emicizumab exposure was predicted using a previously developed population pharmacokinetic model. Bleeding event data were transformed into daily bleed frequencies and analyzed as count data [7,8] using a PKPD model implemented in NONMEM version 7.3 (ICON Development Solutions), with a small run-in METHOD=SAEM to obtain a solid starting position for the subsequent main estimation run using MCMC Bayesian. Models with Poisson, generalized Poisson, and negative binomial (NB) distributions were fit to the data and assessed. Several forms of exposure-response relationships were tested: linear, all or nothing, power and E_{max} models. After selection of an appropriate structural model, the following covariates were tested on all exposure-response model parameters: adjunctive hemophilic treatment (episodic/prophylactic), FVIII inhibitor status (yes/no), FIX and FX concentration at baseline, baseline ABR, as well as demographic covariates. A stepwise procedure was implemented to screen the covariates. Candidate covariate models were then compared by Objective Function Value (OFV), Akaike Information Criterion (AIC), and precision of parameter estimates. The final model was subjected to a Visual Predictive Check (VPC) and subsequently used to simulate the progression of ABR over time. The simulation results were summarized in the form of change from baseline and fraction of bleed free patients.

Results: The generalized Poisson distribution (characterized by two parameters λ and ω) provided the best description of the data, although low differences were seen with the NB distribution. The best fit model included an E_{max} relationship for the effect of emicizumab concentrations on the parameter λ, which described the mean daily bleed frequency. The bleed frequency was estimated to be mildly over-dispersed between patients, as indicated by the dispersion factor (ω) estimate. The mean values (%Relative Standard Error) for λ, ω, maximum treatment effect, and EC_{50} were 0.0356 (8.4%), 0.0244 (19%), 0.979 (1.1%), 2.72 ug/mL (20%), respectively. The estimated E_{max} corresponds to 97.9% reduction of bleed frequency. The

inter-individual exponential variability of λ was 108%. No significant covariates were found. The VPC showed good agreement with the data.

The model was then used to simulate bleeding count over 1 year under different treatment regimens for a large Phase 3 trial with 300 patients. The observed daily mean concentrations at the intended therapeutic dose of 1.5 mg/kg were around 50 µg/ml. The simulated mean bleeding count at 50 µg/ml was 2, which corresponds to a 91% reduction compared to no emicizumab prophylaxis.

Conclusions: Occurrence of bleeding events was described well by a generalized Poisson model, and showed important reduction of the endpoint with increasing emicizumab concentrations following an Emax relationship. The suggested therapeutic dose of 1.5 mg/kg is predicted to provide a 91% mean reduction of ABR compared to no emicizumab prophylaxis, which is close to the estimated maximum effect.

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II-60: *Niclas Jonsson* Increasing the efficiency of the covariate search algorithm in the SCM

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Objectives: To compare the efficiency of the legacy SCM covariate search algorithm [1] to the new SCM+ algorithm.

Methods: The SCM+ algorithm was implemented as a wrapper on top of PsN's SCM program [2]. SCM+ seeks to reduce the legacy SCM run times for covariate searches by adaptive scope reduction (ASR), constrained number of function evaluations, and the CTYPE=4 termination option in NONMEM.

Briefly, ASR uses the outcome from prior search steps to reduce the search scope by removing parameter-covariate combinations with low potential of being included in the final model. When the forward search is finished and before the backward exclusion phase starts, the removed parameter-covariate combinations are re-tested.

To avoid situations with excessive run times without any real progression in the objective function value (OFV) towards convergence, the allowed maximum number of function evaluations (MAXEVAL) in NONMEM is reduced. The reduction in MAXEVAL is based on the number of function evaluations required in the base model without any covariates.

In a similar spirit, the CTYPE=4 option in NONMEM is used, which bases the termination only on OFV (and not the default combination of OFV and parameter gradients, etc). The rationale for the reduction of MAXEVAL and the use of CTYPE=4 is that the SCM algorithm is driven solely by differences in OFV and any factor that increases run-times without impacting OFV should be avoided.

Two real data examples were used to compare the efficiency of the algorithms. Both are phase 3 pharmacokinetic data sets, including data from 1628 and 370 subjects, respectively. In the latter example, the data set was a subset of the original data set to manage run-times. The first model, which has previously been published [3], was implemented using differential equations and the second model included inter-occasion variability from 9 occasions.

Performance was measured as the required total number of function evaluations and total run-times under assumptions of different degrees of computational resource constraints. The search scope for the two data sets included 24 and 57 parameter-covariate relationships,respectively.

Results: Both search algorithms resulted in the same final covariate models. Overall, the SCM+ algorithm required 54% less function evaluations (both examples), compared to the legacy SCM, to establish the final model. Assuming single threaded NONMEM execution, the SCM+ searches required 56% and 49% less time for each of the two data sets, respectively, compared to the legacy SCM searches. Without computational resource constraints, a situation which is maximally beneficial for the legacy SCM search, the SCM+ searches still required less time (43% and 45% less time).

Conclusions: The SCM+ algorithm has the potential to reduce the run-time requirements of covariate searches by more than 50% compared to the legacy SCM search algorithm. This is accomplished by

reducing the number of times that non-significant parameter-covariate combinations are tested and by accepting that the covariate selection decisions are based on slightly different, but for the task at hand more relevant, convergence criteria, compared to the default criteria in NONMEM.

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II-61: *Siv Jonsson* Sample size for detection of drug effect using item level and total score models for Unified Parkinson's Disease Rating Scale data

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Objectives: The aim of this investigation was to estimate the sample size required to reach 80% power for detection of a drug effect using an item response model (IRM) and a total score model (TSM), both describing longitudinal 44-item Unified Parkinson's Disease Rating Scale (UPDRS) data in advanced Parkinson's disease (PD) patients.

Methods: A longitudinal IRM [1] based on data in early and advanced PD was the starting point. The IRM contains 3 latent variables, for each latent variable a placebo time course described with an exponential model estimating the extent (Extent) and onset rate (Onset) of symptom relief over time, and for all a joint exposure independent symptomatic (SY) drug effect: Baseline+(Extent+SY)·(1-exp[-Onset·time]). In this investigation, the IRM was re-estimated for data from advanced PD patients only, comprising of baseline and longitudinal UPDRS recordings collected in a randomized study comparing ropinirole to placebo as adjunct therapy to L-dopa over 24 weeks at individually titrated doses between 6 and 24 mg/day [2]. For the corresponding data a TSM was developed based on patients with complete records of the 44 UPDRS items. Model estimations were performed using NONMEM 7.3. The Monte-Carlo Mapped Power (MCMP) method [3] implemented in PsN was used for power calculations as follows: both models were re-estimated excluding the SY drug effect, and the individual difference in objective function values between the full (with drug effect) and reduced (without drug effect) models (iΔOFV) were extracted. The observed iΔOFVs were employed in the MCMP. The MCMP was stratified based on treatment, a 5% significance level was applied for 1 degree of freedom (ΔOFV 3.84) and 10,000 Monte Carlo samples were drawn. To support the ΔOFV cut-off used in the MCMP approach, a randomisation test [4] was performed for TSM using PsN: based on only placebo or combined placebo and ropinirole data, 1000 data sets were generated, each with a randomly assigned treatment indicator, i.e. placebo or ropinirole on a 1:1 basis, and for each data set the full and reduced model was estimated.

Results: In total 31,212 (190 patients) and 33,951 (201 patients) UPDRS records from placebo and ropinirole treatment, respectively, were used for the IRM. For the TSM corresponding numbers were 663 (189 patients) and 727 (200 patients) records from placebo and ropinirole treatment, respectively. The newly developed TSM was in agreement with the previous IRM, i.e. exponential placebo time course and an exposure independent SY drug effect. The drug effect was statistically significant ($p<0.001$) with ΔOFVs of -210 and -37 for IRM and TSM, respectively. Type I error rates based on the randomisation test employing sampling from only placebo and combined placebo and ropinirole treated patients were similar, and sampling from all patients indicated that using a ΔOFV cut-off of 3.84 would be appropriate. At the 3.84 cut-off the sample size required for 80% power in detecting a drug effect was 54% lower using IRM compared with TSM. The reduction in required sample size tended to be larger when applying a higher cut-off value, with a sample size reduction of 69% at ΔOFV of 10.8.

Conclusions: The results show that employing IRM in the analysis of UPDRS data is clearly beneficial from a study size perspective compared with a TSM analysis, pointing toward a sample size reduction of approximately 50% for detection of a drug effect with 80% power using the current data set. Previous investigations where IRM has been compared with alternative models in PD and other disease areas

reported reductions in sample size varying from 18% to 49% [5-8]. The special MCMP approach taken here is beneficial given the use of observed iΔOFVs, but due to the low number of patients the estimated sample size is expected to be less precise [3].

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II-62: *Felix Jost* Gauss-Newton algorithm for parameter estimation of nonlinear mixed-effects models

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Objectives: Solving (nonlinear) least squares problems (LS problems) with a Gauss-Newton (GN) algorithm is a state-of-the-art approach and the algorithm's benefits are mathematically proven, since GN algorithms provide reliable estimates, not affected by residuals compared to Quasi-Newton (QN) and Newton algorithms.

In NONMEM, the individual parameters ETA are estimated by a GN algorithm, whereas the population parameters THETA, OMEGA and SIGMA are estimated by solving an optimization problem using a variable metric method [1] (QN Method [2]).

The resulting Hessian matrix contains residual-dependent terms, which can drive the iterative optimization procedure into solutions with undesired properties, such as solutions which are strongly influenced by large residual terms in the Hessian matrix.

For this reason, we propose a GN algorithm for the first-order (FO) and first-order conditional estimation (FOCE) approximation of parameter estimation problems for nonlinear mixed-effects models. The algorithm is implemented as a prototype in the software CasADi [3]. CasADi is a symbolic framework for automatic differentiation and numerical optimization with interfaces e.g. to ODE (CVODES and IDAS) and NLP (IPOPT, SNOPT, BLOCKSQP) solvers.

Methods: In a first step, we compared Hessian matrices from a Newton and GN algorithm for LS problems in terms of the residuals' influence on the Hessians' positive definiteness. Therefore, we solved 1000 LS problems for a one-compartment pharmacokinetic model with first-order absorption and oral administration of 320 mg theophylline published in [2].

Based on the results from the first step, we propose a GN algorithm for parameter estimation of nonlinear mixed-effects models. We reimplemented NONMEM's FO and FOCE methods [1,2,4] as a prototype in CasADi and modified the standard algorithm towards a GN algorithm. As Hessian matrix, the approximated population Fisher Information Matrix from [5] is implemented and passed to the interior point algorithm IPOPT [6] interfaced in CasADi [3].

We validated our FO and FOCE reimplementation by comparing parameter estimates, objective function values and Hessian matrix values from NONMEM's FO and FOCE method for two examples.

We used the theophylline model [2] consisting of 12 patients with 10 measurements each (interindividual variability implemented on volume of distribution, elimination rate and absorption rate constant, combined error model for residual variability and full OMEGA matrix) and a one-compartment dummy example with single intravenous bolus administration for 10 subjects with 2 measurements each (interindividual variability implemented on eliminate rate constant, additive error model for residual variability) from [4].

Finally, we tested our new GN FO method by comparing parameter estimates, objective function values and the Hessian matrix dependence on residuals for the theophylline model.

Our GN FOCE method was tested by estimating parameters for the dummy example and comparing the objective function values from our GN and QN FOCE algorithm with those obtained from NONMEM.

Results: The results of the 1000 LS problems demonstrate the superiority of a GN algorithm with respect to the Hessian matrices' independence of residual-containing terms.

Our reimplementation of NONMEM's FO and FOCE method was successfully validated in terms of almost identical objective function values with respect of the two published examples.

The benefit achieved from our GN algorithm applied on the FO approximation is shown using the theophylline example, in which the Hessian matrix from the GN algorithm compared to the Newton algorithm is not affected by large residuals within the solution.

For the dummy example our QN and GN algorithms converge to the same solution which slightly deviates, with a 0.36 smaller objective function value, from the reference solution from NONMEM.

NONMEM: sum(OBJ_i) = sum(8.56, -1.04, -2.04, 1.78, -2.07, -2.27, -1.69, -1.93, -2.18, -1.37) = -4.25

QN/GN: sum(OBJ_i) = sum(9.03, -1.13, -1.99, 1.88, -2.24, -2.37, -1.92, -2.02, -2.34, -1.51) = -4,61

Conclusions: GN algorithms are a promising alternative to QN and Newton algorithms for parameter estimation of nonlinear mixed-effects models, as the Hessian matrix, and thus the computed solution, is not affected by random residual terms. Therefore, we provide a prototype reimplementation of NONMEM's FO and FOCE method in CasADi, which allows to choose between a Newton, QN and GN algorithm.

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II-63: *Astrid Jullion* Dosing Regimen selection supported by population PKPD model of thrombocytopenia

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Objectives: The aim of this work was to develop a mechanism-based pharmacokinetic-pharmacodynamic (PK/PD) model that describes the longitudinal time-course of platelet changes in patients treated with the p53-HDM2 protein-protein interaction inhibitor HDM201, and to apply it to support the identification of an optimal dosing regimen that would be tolerated for at least six treatment cycles.

Methods: Plasma concentrations, platelet and platelet transfusions data were obtained from an on-going phase I study on patients with p53 wild-type solid tumors. In this first in human study, four oral regimens are being investigated: Q3W, day 1 and day 8 of a 4-week cycle, QD 2 week on/2 weeks off in a 4-week cycle, and QD 1 week on/3 weeks off in a 4-week cycle. Delayed thrombocytopenia is the primary reported dose limiting toxicity, often having an impact on long-term treatment sustainability with patients needing dose reductions and/or interruptions. Plasma drug concentrations and platelet data were fitted in a two-step approach using non-linear mixed-effects modeling implemented in Monolix 2016R1. The PK/PD model for thrombocytopenia was modified from Friberg et al. (2002) [1].

In a first step, the PK/PD model has been simulated using a Shiny application developed on R-3.2.3 [2,3] to graphically explore the platelet profiles under different regimens, and to derive key metrics such as time to thrombocytopenia event, recovery time and percentage of patients developing grade 3/4 thrombocytopenia during the 6 first treatment cycles. In a second step, optimization of the drug dosing regimen has been performed using the methodology described in Meille C et al, 2016 [4] extended to take into account inter-patient variability. Optimization criterion was selected as the maximum total drug per cycle (assuming efficacy schedule independency), while complying with predefined clinical constraints on platelet counts. For that purpose, a set of possible dosing regimens has been defined with daily dose amount ranging from 1mg to 500mg and number of days of administration ranging from 1 to the cycle length resulting in a simulations matrix. Then, platelet profiles of 500 virtual patients have been simulated over 6 cycles. In a final step, the proportion of patients with grade 4 thombocytopenia during the first 6 treatment cycles and the total dose amount per cycle have been derived and the most favorable dosing regimens identified.

Results: The concentration-time course of HDM201 was best described as a one-compartment model with a delayed zero- and first-order absorption process, and linear clearance (Cl/F). Body weight was identified as a continuous covariate showing significant influence on the central volume (V/F). The modifications from the model of Friberg et al. (2002) [1] were (1) to include a drug action decoupled from systemic feedback, and (2) to introduce an indirect drug effect on early proliferative cells and on systemic regulation through an effect compartment. In addition, platelet transfusion events were implemented as platelet infusions. Simulations matrix suggest that distributing the total dose in a concentrated period allows reaching a larger total dose per cycle while respecting the constraints on safety.

Conclusions: This work suggests a methodology where a population PKPD model of safety endpoint can be used to support dosing regimen selection, satisfying clinical constraints while maximizing the dose. Possible extension could be to optimize efficacy through a PKPD model on tumor growth in clinics.

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II-64: *Yunseob Jung* A population pharmacokinetic model of methotrexate in Korean people

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Introduction: Methotrexate is a drug for treatment of cancers and autoimmune diseases. To our knowledge, several population pharmacokinetic models have been built in Chinese [1] and Western people [2] but there was no model developed in Korean people. Furthermore, current dosing regimen of methotrexate has a limitation because it was only based on body size such as body surface area (BSA) and was not individualized based on other factors such as age.

Objective:

- Develop a population PK model of methotrexate in Korean people
- Develop new dosing regimen of methotrexate for Korean people

Methods: PK data were acquired from electronic medical records in Yonsei Severance Hospital from 2005 January to 2016 January. We excluded data with sampling time more than 120 hr, intrathecal injection and no duration information. The total number of subjects and samples used for analysis were 188 and 1544, respectively. Subjects had diseases including leukemia and non-Hodgkin's lymphoma. Inter-occasional variabilities were considered in modeling. Theory-based allometry was assumed in incorporating weight into PK parameters [3]. After developing a basic structural model, we explored possible covariate-parameter relationships and developed a covariate model. In continuous covariates, those were centered to median values. Then, multivariate covariate seletion was performed using stepwise covariate modeling with likelihood ratio test at significance level of $p < 0.01$ for forward addition and $p < 0.001$ for backward deletion. Data exploration and model building was carried out using R ver 3.3.3 and NONMEM ver 7.3.

Results: A two compartment model with 1st order elimination was chosen for the basic structural model. Based on that structural model, we chose and developed the covariate model. Significant covariates were age on peripheral volume of distribution, age and serum creatinine on clearance. The structural parameter estimates were 36.39L for central volume of distribution, 26.27L for peripheral volume of distribution, 16.6 for clearance and 0.831 for intercompartmental clearance. The coefficients about covariate-parameter relationships were -0.241, -0.008 and -0.317 in age on peripheral volume of distribution, age on clearance and serum creatinine on clearance, respectively. The inter-individual variabilities (CV%) were 27.2% in peripheral volume of distribution and 31.0% in clearance. The inter-occasional variabilites (CV%) were 92.1% in central volume of distribution, 193.0% in peripheral volume of distribution, 84.2% in clearance and 182.8% in intercompartmental clearance. The proportional residual error (CV%) was estimated to be 41.9%. Standard errors about parameters were all less than 30%. Based on the finally developed covariate model, periphreal volume of distribution decreases by age and clearance decreases by age or serum creatinine. The model adequately described the time course of observed concentrations.

Conclusions: We successfully built a population PK model of methotrexate in Korean people. By a population PK model, we can develop new dosing regimen for Korean patients with hematologic malignancy according to characteristics of a patients.

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II-65: *Fabian Jung* Evaluation of release techniques for nanocarriers on the basis of IVIVC-PBPK modeling

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Introduction: The drug release kinetics is one of the significant factors influencing the efficacy of nanocarriers. Often the *in vitro* release studies are exploited to estimate formulation characteristics, mechanism of drug release, *in vivo* release etc. [1]. However, not much attention has been devoted to assess favorability of different *in vitro* release techniques for studying release from specific nanocarriers. In current study, we have attempted to determine the most appropriate *in vitro* release test to assess selected nanocarriers containing hydrophobic drug for an accurate indication of an *in vivo* drug release.

Objectives: Aim of the current work was to compare two methods for testing the drug release from nanoparticles (viz. dialysis using dispersion releaser (DR) technique and filtration). For this purpose we have employed physiologically based pharmacokinetic (PBPK) model by studying the effect of *in vitro* parameters on the *in silico* profile. As a model formulation, flurbiprofen-loaded poly (?-caprolactone) (PCL) nanocarriers was chosen [2].

Methods: The DR technique utilizes a device fitted on USP II, which separates free drug molecules from nanoparticles by accelerated dialysis whereas the filtration method utilizes filtration through a filter membrane. The two biorelevant *in vitro* drug release methods were compared based on their respective release profiles as well as impact on the *in silico* simulations. During release testing, biorelevant media were used to simulate the human gastric and intestinal conditions. The observed *in vitro* release profiles were fitted in the RPT model [3]. The resulting *in vitro* parameters (m and b value) and permeability data from literature [4] were used to simulate absorption of the drug. The PK parameters which are required for monomolecular drug distribution and elimination were extracted from literature [5]. The model consisting of 9 compartments, which was equipped to calculate the drug flux, was developed using Stella Architect® .To validate the model, simulated profile of a marketed flurbiprofen tablet (100mg, Mylan) was compared with its observed *in vivo* profile [6, 7]. Additionally, the simulated and observed non-compartment PK parameters were compared by applying bioequivalence criteria. To predict the PK of PCL nanocarriers, the results of both techniques were evaluated using the PBPK model. Further, a partial sensitivity analysis was conducted by varying the release rate (±10%).

Results: In *in vitro* studies, both methods led to a substantial drug release i.e. 91.0 ± 5.3 % for filtration and 100.9 ± 4.1 % for the DR technique respectively. During validation, the PBPK model was able to reflect the *in vivo* situation when compared with mean profile and bioequivalence criteria. Although with the *in silico* model, both techniques produced similar results, the release data obtained with the DR technique revealed higher sensitivity *in vitro* and in the simulated profiles as compared to filtration technique.

Conclusions: In summary, the filtration technique enables a rapid testing with suitable simulations in the early stages of research whereas the DR based simulations detected changes in the release rate more efficiently throughout the process. Therefore based on our results the DR technique proved to be more appropriate in formulation development and quality control as compared to the filtration technique. Furthermore PBPK modeling demonstrates itself as a useful tool to estimate the influence of minor changes in *in vitro* results on the actual *in vivo* performance.

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II-66: *Tobias Kanacher* Development of a whole body physiologically-based pharmacokinetic (PBPK) model for inhaled salmeterol to predict interactions with CYP3A4 inhibitors

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Objectives:

To develop a whole body PBPK model for salmeterol, capable of describing the pharmacokinetics (PK) of salmeterol following inhalation via the DISKUS® inhaler. Because this model is intended to be used as victim drug model in drug-drug interaction (DDI) simulations, close attention was paid to the precise estimation of the following aspects:

- Fraction absorbed from lung to the systemic circulation and subsequent metabolism in the liver

Fraction swallowed, which then can be subject to either pre-systemic metabolism via CYP3A4 [1] in the intestine or the liver.

Methods:

A PBPK analysis using the Open Systems Pharmacology (OSP) Suite 7.2.1. was conducted in a stepwise middle-out approach. No PK data in humans after intravenous (i.v.) dosing and only very limited data following oral (p.o.) administration to humans and different animal species were available [2]. Thus in the first step, literature mean concentration-time data from healthy volunteers inhaling a single dose of 50 µg salmeterol with simultaneous gavage of charcoal [3] to supress oral absorption were used to define distribution and clearance.

As the exact fraction deposited in the lungs and subsequently absorbed from there is unknown, different scenarios with fractions deposited ranging 10%[4] – 25%[5] were investigated. Further the effect of diverse ways of describing lung absorption were evaluated: directly from the lung cells with and without first order release or from an additional alveolar lung fluid (ALF)[6] compartment.

In the second step, data from an in-house clinical study [7] with inhaled salmeterol by healthy volunteers in the same dose and conditions but without charcoal were used to identify intestinal permeability and fraction metabolised in gut.

Model evaluation was performed with clinical data from healthy volunteers inhaling 50 µg or 100 µg salmeterol twice daily for seven days [8], [9].

Finally, the model was used to predict AUC and Cmax of salmeterol following the simultaneous oral administration of a strong CYP3A4 inhibitor. This was done by either assuming a fixed 90% reduction of the CYP3A4 clearance of salmeterol or co-administration of itraconazole, considering its dynamic concentration-time course.

Results:

A scenario-driven middle-out approach led to a robust PBPK model structure being able to describe mean PK parameters of salmeterol in healthy volunteers following inhalation.

The models with lung absorption via lung cells with first order release or via absorption from ALF resulted in equivalent estimations for distribution and clearance and matched the physicochemical properties of salmeterol better than the model with lung absorption via lung cells without first order release.

The successful model included the following assumptions:

- fraction of dose released from the device is assumed to be 90%, of this the fraction
    - deposition in the lung can range from 10% - 25% and is absorbed by a fast first order kinetics
    - Fraction swallowed ranges accordingly from 80% – 65%
- fraction mucociliary cleared can be neglected
- no differentiation between different lung absoprtion sides
- salmeterol mainly metabolised by CYP3A4 in gut/liver (not metabolism in lung)
- renal excretion of salmeterol is negligible (<5% dose)

Further investigation using the scenario with 20% fraction deposited to lung in population simulations with 2000 virtual individuals suggested, that variable efficiency of inhalation largely contribute to the inter-individual variability of salmeterol PK.

A DDI simulation with 90% reduced CYP3A4 clearance to mimic the effect of a strong CYP3A4 inhibitor resulted in predictions of AUC and Cmax ratios within two-fold range with clinical observations where salmeterol was given with and without ketoconazole as perpetrator. DDI simulations where itraconazole was dynamically coupled with the salmeterol model further confirmed the model.

Conclusions:

This is the first whole body PBPK model describing human PK of salmeterol after inhalation that can be used for predictions of DDIs with orally given strong CYP3A4 inhibitors.

Using a middle-out approach based on a limited human dataset from literature sources and in-house data successfully lead to a robust model structure.

The model was confirmed with salmeterol PK after multiple inhalations of different doses in humans.

This example demonstrates how PBPK models can bridge limitations in data by inclusion of prior knowledge and investigation of alternative routes of applications.

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II-67: *Iasonas Kapralos* Population Pharmacokinetics of Anidulafungin in ICU patients

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Objectives: Anidulafungin (ANF), an echinocandin-class antifungal, is considered to be initial therapy for invasive candidiasis. Although echinocandins have shown an ideal pharmacologic profile, with limited adverse reactions and drug-drug interactions, as well as low exposure variability among patient populations, dose optimization may be considered, in the context of the increasing antifungal resistance and the unstable nature of ICU patients. Thus, aim of our study is to develop a pharmacokinetic model, which describes Anidulafungin pharmacokinetics in critically ill patients, and identify covariates.

Methods: Pharmacokinetic data were obtained by two clinical studies, conducted at the Intensive Care Units of Attikon and Ippokrateion University Hospitals of Athens. A total of 192 plasma samples were collected from 13 patients, receiving ANF upon proven invasive candidiasis, as an empiric treatment or prophylaxis. ANF was administered as a short-term intravenous infusion in a dose of 100mg once a day, while 9 patients received a loading dose of 200mg on the first day. A dense sample strategy, which included a pre-dose sample and 5 to 7 samples in a 24 hour time interval after the start of infusion, was followed. Plasma Anidulafungin concentrations were measured with a validated HPLC-fluorescence plasma assay method. We performed the population PK analysis, using non-linear mixed effects modelling in NONMEM® (version 7.3) and the FOCEI method. The development of the base model included the implementation of 1-compartment, 2-compartment and 3-compartment structural PK forms, as well as the use of additive, proportional and combined models to describe the residual variability. Inter-individual variability (IIV) was modelled using an exponential function, and then subsequently an inter-occasion variability (IOV) component was taken into consideration. Covariates including body weight, height. BMI, BSA, Creatinine Clearance and age, in addition to ICU specific covariates as the SOFA Score and APACHE II score were examined. Models have been evaluated based on the criteria of successful minimization, assessment of diagnostic plots and visual predictive checks, and bootstrap as a measure of the estimation precision. The selection of the covariates on the PK parameters was based on the Likelihood Ratio Test with a significance level of 0.01.

Results: A two-compartment model, with first-order elimination and proportional residual error, was found to best describe the time course of plasma Anidulafungin concentrations in the specific population. The estimates of the PK parameters (inter-individual variability calculated as CV %) were: Clearance (CL) = 0.816 L/h (37.4%), central volume of distribution (V1)= 9.96 L (30.1%) , peripheral volume of distribution (V2)= 22.5 L/h (39.2%) , and inter-compartmental clearance (Q)= 5.8 L/h (40.1%). A significant inter-occasion variability was estimated for Clearance and Central Volume to be 28.3 (%CV) and 38.5 (%CV) respectively. SOFA score was found to be statistically significant covariate for CL and V1. An increase in SOFA score from 7 to 17 is found to result in a 52.3 % reduction on the Clearance estimation.

Conclusions: A model was developed for Anidulafungin PK in ICU patients, based on dense data. The pronounced inter-occasion variability in the exposure of ICU patients to ANF which was observed, challenges the ability to individualize the dose of Anidulafungin in critically ill patients. Further analysis,

could examine the influence of time-varying covariates on PK parameters and explain the observed inter-occasion variability.

II-68: *Eleni Karatza* Mathematical modeling of gastric emptying: a joint model for losartan and its active metabolite EXP-3174

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Objectives: Develop a joint pharmacokinetic model, describing the kinetics of losartan (LOS) and its active metabolite (EXP-3174) that seem to be significantly affected by gastric emptying.

Methods: LOS and EXP-3174 plasma concentration (C) – time (t) data were obtained from a single dose, 2x2 bioequivalence study comparing two immediate release oral products in 25 men and women. Concentrations were expressed in pmoles per mL for the joint modeling of LOS and EXP-3174. Non-linear mixed-effect modeling was applied and a variety of pharmacokinetic models were examined. In order to mathematically describe the delayed and variable appearance of LOS and EXP-3174 in plasma, resulting in oscillations of the concentration, several approaches were explored including: the use of gastrointestinal pseudo-compartments, delay differential equations, time-dependent gastric emptying, and periodic gastric release using sinusoidal functions. Models tested were evaluated in terms of their physiological relevance and goodness-of-fit criteria. Several error models were evaluated, whereas the period and treatment effects were tested as potential covariates. The entire computational work was implemented in Monolix 2016R1.

Results: The disposition of LOS was best described by a two-compartment model preceded by another compartment representing a pre-absorption gastro-intestinal compartment. For the metabolite EXP-3174, a one-compartment model led to the optimum performance. Delay differential equations were found to be the most appropriate approach to mathematically describe the oscillations [1] observed in the plasma concentration of LOS and EXP-3174. Indeed, both the absorption rate of LOS and the metabolite formation rate were expressed by first order constants integrated in a system of delay differential equations. The pharmacokinetic parameters derived for losartan were the first order gastric emptying constant (Kg = 3.98 h^{-1}), the absorption rate constant in the central compartment (Ka = 1.38 h^{-1}), the absorption lag time (tau1 = 0.131 h), the apparent volume of distribution of the central (Vp1/F = 50.3 L) and peripheral (Vp2/F = 211 L) compartment, the apparent clearance from the central compartment (CL/F = 125 L/h), and the inter-compartmental clearance (Q/F = 165 L/h). For the active metabolite, EXP-3174, the formation rate constant (Km = 0.455 h^{-1}), the formation lag time (tau2 = 0.281 h), the apparent volume of distribution (Vm/F = 16.4L), and clearance (CLm/F = 4.14 L/h) were derived. Based on the findings of this study, it can be generally deduced that similar models with delay differential equations can describe the pharmacokinetics of orally administered drugs with high solubility and low permeability, which are affected by gastric emptying as LOS. Application of a combined error model led to the optimum performance for both LOS and EXP-3174, whereas no statistically significant difference was observed in the performances of the two drug products.

Conclusions: The most appropriate joint pharmacokinetic model for LOS and EXP-3174 plasma C-t data consisted of a two-compartment model for LOS and a one-compartment model for EXP-3174, using delay differential equations for both the absorption rate and the metabolite formation rate.

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II-69: *Yuri Kheifetz* Integral individualized model of hematopoiesis explains and predicts joint dynamics of thrombocytes, granulocytes and lymphocytes under different chemotherapeutic and adjuvant treatments scenarios

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Objectives:

Leukopenia and thrombocytopenia are among the major side-effects of cytotoxic cancer therapies. Maturation of different blood cell lines are interdependent and influenced from stem-cells-niches supporting osteoblasts. The development of individual therapy adaptations is a non-trivial task since thrombocytopenic and leukopenic risks depend on many therapy-associated and individual factors. To solve this task we revised our biomathematical model of average granulopoiesis under chemotherapy or growth factor treatments (Scholz et al. 2004, 2013), combined it with our novel individualized model of thrombopoiesis (Kheifetz et al. 2017; Kheifetz et al. 2018) as well as with a model of osteoblasts/osteoclasts dynamics of other group (Komarova et al. 2003) and our novel model of lymphopoiesis. We implemented it in a software-tool usable for therapy management.

Methods:

We performed bio-mechanistic modelling of the dynamics of bone marrow hematopoietic and mature circulating cells by ordinary differential equations. We introduced quiescent states for stem and progenitor cells, whose activation is mediated by interactions with osteoblasts, growth factors thrombopoietin (TPO) and granulocyte-colony stimulating factor (G-CSF). Attached mechanistic PK/PD models consider injections of growth factors as well as of cytotoxic drugs. Short-range treatment effects influence proliferating blood-cells precursors, while both chemotherapy and G-CSF induce a long-term depletion of osteoblasts reducing the supporting capacity of the bone marrow. Our novel lymphopoiesis model describes short- and long-living lymphocytes, circulating between blood and peripheral compartments and originating from hematopoietic stem cells. We fitted 33 individual and 50 population parameters using simultaneously data from 11 studies measuring 19 different biological outcomes (cell counts of platelets, neutrophils, lymphocytes, leukocytes, megakaryocytes of different ploidies, osteoblasts, banded and segmented granulocytes; concentration of granulocyte-colony-stimulating factor (G-CSF), thrombopoietin (TPO) and prednisone). These 11 studies contained either individual or averaged data on hematopoiesis under five different chemotherapy regimens (CHOEP, BEACOPP, docetaxel, paclitaxel, carboplatin) and stimulatory treatments by TPO, filgrastim, pegylated filgrastim (synthetic variants of G-CSF), prednisone and transfusion of platelets or stem cells. We applied our innovative parameters estimation methodology, which has been developed earlier during a versatile fitting of our individualized thrombopoiesis model (Kheifetz et al. 2018). This methodology is based on virtual participation of patients from clinical studies in other experiments measuring different biological features.

Results:

Our model qualitatively and quantitatively explains major mechanisms of hematopoiesis. We described a negative synergism between G-CSF and TPO competing on a choice between granulopoietic and thrombopoietic differentiation alternatives of progenitor cells. According to several independent studies, we upgraded our model by direct stimulating effects of G-CSF and TPO on quiescent stem and early

progenitor cells. We have found that multi-cyclic chemotherapy significantly reduces transit times for megakaryocytes. The long-term decrease in average platelets and leukocytes levels during multi-cyclic chemotherapy was attributed to interactions between osteoblasts, quiescent and active progenitor cells compartments. These slow changes are responsible for strong intra-individual variability of blood cells' nadirs and consequently of chemotoxicity through treatment cycles. Incorporation of mechanistic model of osteoblasts and osteoclasts improved significantly the predictive potential of the thrombopoiesis model (Kheifetz et al. 2018). Our model described well few regimens of high-doses chemotherapy accompanied by bone-marrow transplantant.

Conclusions:

We successfully established a comprehensive mechanistic model of human hemathopoiesis perturbed by a wide spectrum of chemotherapies as well as of supportive treatments. It allows individual simultaneous predictions of degrees of thrombopenia, neutropenia, lymphocytopenia as well as of bone marrow injury with superior accuracy compared to statistical or semi-mechanistic competitors. This model has been realized in a tool supporting individualized decision making and therapy adaptations by physicians during multi-cyclic cancer treatments.

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II-70: *Yun Kim* A population pharmacokinetic analysis of voriconazole according to CYP2C19 phenotype in healthy subjects and patients

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Introduction: Voriconazole is a broad-spectrum antifungal agent for the treatment of invasive aspergillosis. High variable and non-linear pharmacokinetics of voriconazole has been found to be caused by many factors including CYP2C19 polymorphisms, demographics, drug-drug interactions, and liver function. Above all, CYP2C19 phenotype is an important intrinsic determinant of voriconazole exposure. However, the effect of CYP2C19 phenotype on voriconazole exposure was not quantitatively identified.

Objectives: The aims of this study were to develop a population pharmacokinetic model of voriconazole, and to evaluate the demographic, CYP2C19 phenotype, drug-drug interaction, and liver-function related determinants of voriconazole exposure.

Methods: A population pharmacokinetic model was developed using 1579 voriconazole concentrations in 93 healthy male subjects at first. Then, 249 concentrations in 100 patients were used for final model development with the some healthy-driven fixed parameters. Subjects received single and multiple intravenous (IV) and/or oral dosing of voriconazole. The First-Order Conditional Estimation with Interaction estimation method was used with NONMEM (version 7.3). The effects of demographics, liver- and kidney-function related parameters, and CYP2C19 phenotype on the pharmacokinetics of voriconazole were evaluated.

Results: A three-compartment model with an inhibition compartment adequately described the time-concentration profiles of voriconazole. The inhibition compartment reflects the auto-inhibition of voriconazole metabolism. The absorption kinetics of voriconazole was best described by first-order absorption with lag time. The typical values of the model are as follows: clearance (45.3 L/h), volume of distributions (V_2, V_3 and V_4, 35.7, 58.9 and 25.4 L, respectively), inter-compartmental clearances (Q_2 and Q_3, 10.9 and 54.6 L/h, respectively), first-order absorption rate constant (k_a, 1.23 /h) with lag time (0.237 h), and bioavailability (F, 0.876). Clearance was inhibited over time to 16.2 % of its original value dependent on the concentration in an inhibition compartment. Weight was found to be a significant covariate for the CL, Q_2, and V_3 of voriconazole. CYP2C19 phenotype had a significant effect on the exposure of voriconazole. The extent of the phenotypic effect was derived from healthy volunteers and fixed for the final model development. The CL estimates in CYP2C19 IM and PM decreased 17 % and 53 % compared to that in extensive metabolizer (EM). CL also decreased 47 % in the patients with liver-function test grade (≥3). The remaining CL fraction estimates in CYP2C19 IM and PM decreased both approximately 40 % fold over that in EM.

Conclusions: The pharmacokinetic parameters of voriconazole were well described by the developed population model. This study was first attempt to mechanistically explain the nonlinearity in voriconazole pharmacokinetics using an inhibition compartment model. The model in the contribution of CYP2C19 and liver-function to the pharmacokinetic variability of voriconazole can be served as a tool to predict the systemic exposure of voriconazole, thus providing a rationale for individualized optimal dosing to improve clinical outcome.

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II-71: *Yu Kyong Kim* A Prospective Population Pharmacokinetic Study for Recommendation of Prophylactic Fluconazole Dosage Regimen in Preterm Infants

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Objectives: Several reports have been suggested that prophylactic use of antifungal agents such as fluconazole reduces mortality rate in preterm infants with extremely low birth weights via suppression of invasive systemic candidiasis causing *Candida* colonization [1]. However, the human data for appropriate prophylactic dosage regimen of fluconazole in preterm infants are limited; hence the off-label uses based upon empirical knowledge of the paediatricians. This study was to construct a population pharmacokinetic model for prophylactic fluconazole in Korean preterm infants for suggestion of optimal dosage regimen.

Methods: By using a nonlinear mixed-effects method in NONMEM (version 7.4) [2] a population pharmacokinetic model was developed using the prospectively collected 301 fluconazole plasma concentrations from 75 premature infants (post-natal age range of 3-8 days, gestational age of 23.7-35.7 weeks and body weight of 0.54-1.49 kg) who admitted to the neonatal intensive care unit of Seoul National University Children's Hospital. Eligible premature infants received intravenous (30 min infusion) or oral 3 mg/kg dose of fluconazole, twice weekly with more than 72-hour dose interval, for 4 weeks. Implementing the First-Order Conditional Estimation with Interaction estimation method, the model was sequentially qualified with basic goodness-of-fit (GOF) diagnostics, visual predictive checks (VPCs) and bootstrapping for evaluation of adequacy and prediction. Simulations were performed investigating different dosing intervals and dosages for optimum regimen that >90% of the simulated data would result in pre-specified efficacious exposure [3].

Results: Fluconazole pharmacokinetic characteristics were well described with a one-compartment linear pharmacokinetic model with proportional residual error. With the following equations, the population clearance and volume of distribution were derived: clearance (L/h) = 0.0219 · (body weight)$^{0.746}$ · (estimated glomerular filtration rate with Schwartz equation for infants with low body weight under 1-year-old/25)$^{0.463}$; volume of distribution (L) = 1.04 · (body weight). The inter-individual variabilities (coefficient of variations, %) of clearance and volume of distribution were 23.8% and 21.4%, respectively. The estimated oral bioavailability of fluconazole was 90.9%. The proposed model was adequate with good precision based on the model evaluation by GOF diagnostics, VPCs, and bootstrapping. The simulated data suggested that at least 6 mg/kg every 24-hour regimen would be necessary to achieve the previously suggested exposure of fluconazole for prophylaxis in preterm infants with glomerular filtration rate range of 10.3 - 46.8 mL/min/1.73m^2.

Conclusions: With the final pharmacokinetic model of fluconazole which adequately described the observed plasma concentration of fluconazole in preterm infants, the model-fitted parameter estimates and simulation allowed suggestion of prophylactic fluconazole dosage regimens in preterm infants.

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II-72: *Hyungsub Kim* Pharmacokinetic and pharmacodynamic modeling of 10% intravenous immunoglobulin and glucocorticoids for adult patients with immune thrombocytopenia

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Objectives: Immune thrombocytopenia (ITP) is acquired thrombocytopenia by platelet destruction caused by autoantibodies. [1] Intravenous immunoglobulin (IVIg) can elevate the platelet count by blocking macrophage uptake of autoantibody-surrounded platelets. [2] Glucocorticoid administration is beneficial for ITP patients by enhancing apoptotic death of autoantibody-producing lymphocytes and downregulation of macrophage activity. [3] The objectives of this study is to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of IVIg-SN 10% in adult ITP patients in conjunction with glucocorticoid co-administration.

Methods: PK/PD data used for this analysis were from a prospective, non-randomized, open-label, single-arm, multi-center phase III clinical trial where 81 subjects intravenously received IVIg-SN 10% at a dose of 1g/kg/day for two consecutive days and 69 subjects completed the study. The response was defined as the achievement of the platelet count (PD marker) of > 50 × 10^9^/L at day 8, and 75.7% achieved the response satisfying the pre-defined non-inferiority condition (70%). PK analysis (25 subjects) was conducted by nonlinear mixed effect modeling implemented in NONMEM using first-order conditional estimation with INTERACTION method. PD analysis was performed using the indirect response model with a precursor pool and for those who received both IVIg-SN 10% and glucocorticoid (prednisolone, methylprednisone, or dexamethasone) the response-surface model for the platelet count was applied.

Results: The PK modeling was conducted, and covariate analysis revealed that sex (male) and body surface area affect PK of IVIg-SN 10% by increasing volume of distribution. Data showed the sharp increase in the IVIg-SN 10% concentration after intravenous administration and gradual decrease ($t_{1/2\beta}$ = 28.9 days). Median time to response was 2 days and mean duration of maintaining response was 9.13 days. Concomitant systemic glucocorticoid administration can increase and maintain the platelet count. The final plasma PK model and response-surface PD model describe the data reasonably well.

Conclusions: The current modeling and simulation analysis characterized the PK/PD of IVIg-SN 10% using the response-surface model of glucocorticoids, which will be useful in identifying the optimal dosing regimens of IVIg-SN 10% and glucocorticoids.

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II-73: *Anne Kümmel* Building predictive longitudinal PKPD models of antimalarial combinations with Phase 2b data

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Introduction: The World Health Organization recommends artemisinin-based combination therapies against malaria. However, the increasing emergence of resistance jeopardizes the efficacy of the current treatments, calling for the continuous generation of new drugs. Medicines for Malaria Venture (MMV) and its partners are developing new drugs and testing new combinations. MMV employs model-based approaches to support selection and progression of individual compounds at different stages of drug development. Recently, the combination of a new compound, artefenomel, with a marketed compound, piperaquine, was tested in patients. For this study, a logistic regression model was built for the fraction of patients with no recrudescence at day 28 as a function of the drug concentrations at day 7 [1]. The model was used to identify covariates driving efficacy and to simulate non-tested dose combinations. However, this model neither provides any information about the time course of parasitemia nor is easily related back to preclinical pharmacology. Also, the ability to extrapolate to different dosing regimens is limited.

Objectives:

- Develop a longitudinal PKPD model, describing the time-course of the parasitaemia after treatment with artefenomel and piperaquine
- Identify significant covariates driving efficacy

Methods: Data from three Phase 2 trials with either artefenomel monotherapy or artefenomel and piperaquine combination therapy was pooled for a stepwise, nonlinear, mixed-effects modeling. First, a PK model for the pooled data was developed and the individual parameter estimates used as regression parameters for the subsequent PD modeling. The PD model described the drug effect with a sigmoidal model linking drug concentrations with parasite clearance. The effect of the combination was the sum of the single drug effects, however, accounting for mutual impact on the maximum effect (Emax) or the potency for one drug (EC50) by the other [2]. The PD model parameters for artefenomel were estimated, and subsequently fixed, based on data from patients treated with artefenomel alone. Interaction parameters were estimated while also estimating the PD parameters for piperaquine or fixing these to values determined in a previous controlled human malaria infection study. Covariates from a preselected set were tested for all PD parameters but the interaction parameters.

Results: The developed longitudinal model described well the observed individual profiles and the fraction of recrudescent patients over time. Region was identified as covariate on the drug effect. Since region was correlated with age and weight, the covariate effect might likewise also be associated with age or weight. Visual predictive checks supported the model's accuracy in prediction of fractions of recrudescent patients both for the overall and for subpopulations of interest. Fixing the PQP PD parameters on values obtained from the PQP monotherapy challenge study led to biologically plausible parameter estimates and simulations.

Conclusions: The good predictive behavior of the developed model demonstrates the power of longitudinal modeling, over other approaches, for supporting dose selection for clinical study design and different

patient populations. Two critical data aspects were highlighted by the analysis: a) availability of monotherapy data for both compounds for combination therapy model building, and b) presence of recrudescence events (treatment failures). In the future, MMV is planning to test both mono- and combination therapy in controlled human malaria infection studies prior to going into patients. This will enable better model-based support of dose and combination selection for Phase II as subtherapeutic doses can be considered, enriching the data with information about treatment failures. Finally, the model will be enriched with patient data as Phase II studies are conducted, and will allow adjustment of doses in specific populations, e.g., children, if required.

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II-74: *Franziska Isabelle Kluwe* Joint model for the characterisation of cefuroxime pharmacokinetics in synovial fluid, interstitial fluid of muscle tissue and plasma

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Objectives: Cefuroxime, a broad-spectrum cephalosporin antibiotic, is routinely administered as preoperative prophylaxis during orthopaedic surgery and for the treatment of septic arthritis. Adequate antibiotic concentrations at the target site of an infection are required for effective prophylaxis or therapy. However, information about target-site pharmacokinetics of cefuroxime is still lacking. The microdialysis technique is a minimally invasive, highly sensitive method to investigate antibiotic target-site concentrations**.** In order to evaluate the pharmacokinetics of cefuroxime after standard dosing in different matrices, including synovial fluid of the knee and interstitial fluid of muscle tissue assessed by microdialysis, the nonlinear mixed-effects modelling approach was used.

Methods: For the model development, data from an open-labelled, single-centre Phase I study (EudraCT: 2012-000379-18), conducted at the Medical University of Vienna, was used [1]. Patients undergoing elective knee arthroscopy (n=10, 8 male, age: 18.7–61.7 years, weight: 58.0–118 kg) received a single postoperative infusion of 1500 mg cefuroxime over 30 min. Plasma samples were taken and microdialysis was performed simultaneously in the synovial space of the knee and in the skeletal muscle of the thigh, using retrodialysis for catheter calibration. For each matrix (synovial fluid, interstitial fluid of muscle tissue and plasma), samples were collected pre-dose ($n_{median/matrix}$=10) and every 30 to 60 min up to 8 h after dosing ($n_{median/matrix}$=110). The samples were quantified via high-performance liquid chromatography and data from all matrices was analysed using R (3.4.3) and NONMEM (7.3.0, with first-order conditional estimation method and interaction option). To assess the model performance, precision of parameter estimates and graphical model evaluation techniques, such as goodness-of-fit plots and visual-predictive checks, were utilised.

Results: A two-compartment pharmacokinetic model with linear elimination adequately described the plasma data. Due to delayed distribution of cefuroxime into the synovial fluid and interstitial fluid of muscle tissue, both –kinetically similarly behaving– matrices were assigned to the peripheral compartment. To account for the extent of cefuroxime distribution into synovial fluid and interstitial fluid of muscle tissue in the model, a tissue distribution factor was estimated for each matrix. Overall, cefuroxime displayed good penetration abilities into both synovial fluid (distribution factor of 1.94) and interstitial fluid of muscle tissue (distribution factor of 1.59) with respect to peripheral concentrations. Cefuroxime clearance was estimated to be 16.5 L/h, the central volume of distribution, intercompartmental clearance and peripheral volume of distribution were 14.2 L, 20.2 L/h and 13.5 L, respectively. Relative recovery estimated during retrodialysis was found to be comparable in interstitial fluid of muscle tissue and in synovial fluid (14.8% and 14.2%). Using an exponential model for random effects, interindividual variability was implemented on clearance, central volume of distribution, relative recovery values and tissue distribution factors, yielding least precise estimates for relative recovery in synovial fluid (67.2 %CV). Residual variability was separately estimated for the different measurement matrices, enabling the dissection of overall residual variability into matrix- and/or microdialysis technique-dependent components.

Conclusions: A joint model simultaneously describing the pharmacokinetics of cefuroxime in synovial fluid of the knee, interstitial fluid of muscle tissue and plasma after single intravenous infusion in patients undergoing elective knee arthroscopy was successfully developed. Overall, cefuroxime displayed good penetration abilities from the peripheral compartment into both synovial fluid and interstitial fluid of muscle tissue. As next step, a covariate analysis will be performed to identify factors influencing the pharmacokinetics of cefuroxime. Ultimately, the joint model incorporating potential covariate effects can be used to perform Monte-Carlo simulations to evaluate the probability of target attainment of the current dosing regimen for different pharmacokinetic/pharmacodynamic targets in the various matrices.

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II-75: *Wojciech Krzyzanski* Implementation of delay differential equations in NONMEM

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Objectives: Models involving delay differential equations (DDEs) are increasingly popular in analysis of pharmacokinetic and pharmacodynamics data. A distinct feature of DDEs is a history that needs to be evaluated in order to determine the change of the state at a current time. This requires additional computational time that makes numerical DDE solvers to run longer compared to analogous solvers for ordinary differential equations (ODEs). Another distinct feature that is poorly handled by available DDE solvers is presence of bolus dosing events that introduces discontinuous input into DDE models and increases computational time. A technique called method of steps (MOS) has been introduced that transforms any system of DDEs into a system of ODEs [1]. A feature that impacts numerical performance of MOS is high dimensionality of ODE systems. Another practical issue is complexity of implementation of MOS into PKPD software. A program DDEXPAND has been developed for coding DDE based models in NONMEM [2]. DDEXPAND applies MOS to translate DDE model equations into a NONMEM control stream that can run using any of available ODE solvers. The objective of this work was to assess numerical performance of MOS implemented in NONMEM by DDEXPAND compared to well established DDE solver dde23 implemented in MATLAB [3].

Methods: Three previously published DDE models were selected for testing the MOS: delayed logistic growth (LOGISTIC), rheumatoid arthritis (RA), and tumor growth inhibition [4]. All models were implemented in NONMEM 7.4 by means of DDEXPAND with ADVAN 13 ODE solver. For each model 100 predictions were simulated for one subject using published typical values without residual variability. The CPU time was recorded for each simulation. Analogously, each model was coded in MATLAB R2017b. The model DDEs were solved by dde23 for an individual subject at 100 observation times identical with NONMEM models. The CPU time was recorded for each simulation. Additionally, each model was implemented in MATLAB using MOS equations based on NONMEM control stream generated by DDEXPAND. The ode45 ODE solver was used to solve model equations. Similarly, 100 predictions were simulated and CPU times were recorded. The mean of 10 CPU times was used as a measure of performance. The same ATOL and RTOL values were used for all solvers. Maximum absolute and relative differences between NONMEM and MATLAB solutions were used as metrics of MOS accuracy. Both NONMEM and MATLAB were run on a PC computer with Intel Fortran compiler v 11.1.

Results: The LOGISTIC model consisted of one DDE with constant past. MOS resulted in 12 ODEs. The mean CPU time for NONMEM was 0.0591±0.0097and MATLAB 0.05830±0.0183 (dde23) and 0.09236±0.0254 (ode45). The absolute and relative errors were 2.27E-03 and 2.28E-04, respectively. MOS became unstable if the number of ODEs exceeded 50. The original RA model consisted of two-compartment PK and three PD DDEs with non-constant past, and two outputs (total arthritic score,TAS, and ankylosis score, AKS). There were 8 MOS ODEs. The simulations were done for placebo, and doses 1, 10, and 100 mg/kg. The mean CPU time for NONMEM was 0.08890±0.0196 and MATLAB 0.7516±0.0537 (dde23) and 0.1794±0.0370 (ode45). The absolute and relative errors for 100 mg/kg were 1.77E-06 and 4.78E-07 (TAS), 8.36E-06 and 6.04E-05 (AKS), respectively. The TGI model consisted of one-compartment with first-order absorption PK, one control PD, and two PD DDEs with constant past, and 5 multiple doses. There were 36 MOS ODEs. The mean CPU time for NONMEM was 0.09360±0.0222 and MATLAB 6.644±0.0511 (dde23) and 0.7396±0.0364

(ode45). The absolute and relative errors were 2.34E-04 and 3.28E-04 (control), 1.46E-04 and 3.1E-04 (treatment), respectively.

Conclusions: For LOGISTIC model NONMEM is equally fast as MATLAB, but it is one order less accurate than MATLAB (accuracy was improved with small increased ATOL and RTOL without significantly affecting computation time). If the number of steps becomes large, MOS might become unstable. For RA model with single bolus injection NONMEM is 8.5 times faster than MATLAB and equally accurate. For TGI model with multiple drug administrations NONMEM is 71 times faster than MATLAB and equally accurate.

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II-76: *Gilbert Koch* Characterization of postnatal sodium fluctuation in very preterm neonates

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Objectives: It is well know that severely ill patients experience substantial fluctuations of serum sodium. Several studies show that large variations of sodium are associated with increased morbidity and mortality in adults [1]. Interpretation of available studies allows the conclusion that serum fluctuations are not only a marker of illness severity, but cause increased morbidity and mortality itself. The situation in the pediatric population and even more in preterm neonates is less clear. However, some studies associate hypernatremia, hyponatremia or sodium variations with increased risk of serious complications such as intracerebral hemorrhage in preterm infants [2-3]. After birth, neonates experience loss of water and can develop hypernatremia, i.e. a rise of serum sodium to a value exceeding 145 mmol/l during the first days of life. Hypernatremia seems to be more frequent in preterm neonates with low gestational age (GA) due to increased water loss. Hyponatremia, i.e. values below 135 mmol/l, may also occur due to renal salt wasting as a result of the inability of immature kidneys to produce adequate urine tonicity. The purpose of this study is to identify factors that influence sodium fluctuations during the first 28 days of life in preterm neonates with GA < 32 weeks.

Methods: This retrospective study included all preterm neonates with GA < 32 weeks, born between 2007 and 2014 at the neonatal unit of the University Children's Hospital in Bern, Switzerland. A descriptive modeling approach based on an indirect response model with a stimulatory effect on sodium production was used to characterize data. Delayed increase of sodium after birth was modeled with a tlag parameter. Initial value of sodium at birth was allowed to be different from steady state value after 28 days. Non-linear mixed modeling in The Monolix Suite 2016 (Lixoft, Orsay, France) was applied to fit data and to characterize covariate effects on model parameters. Continuous covariates were described by non-linear power functions. Secondary parameters, such as predicted sodium peak concentration, were accessed via simulations from the estimated individual model parameters in R (R Foundation for Statistical Computing). Normally distributed values are reported as mean (sd) and others as median [IQR].

Results: A total of 901 preterm neonates with GA of 29.4 [27.4, 30.9] weeks and a total of 20714 sodium measurements were eligible to be included in the study. Inclusion criteria were (i) at least one sodium measurement within the first 24 hours, and (ii) at least two measurements in total. Sodium at birth was predicted to be 133.1 (1.9) mmol/l and similar across GA. Sodium increase started at post-natal age (PNA) of 1.2 (0.6) days and a sodium peak of 143.0 (2.7) mmol/l was observed at PNA of 3.2 (1.5) days. GA and delivery mode (DM) had a significant impact on sodium peak concentration. More precisely, lower GA caused higher sodium peaks (e.g. 145 mmol/l for GA = 24 weeks and 142 mmol/l for GA = 30 weeks) and neonates with spontaneous birth had higher peaks compared to neonates with caesarean section. Approximately after 10-15 days mean sodium concentration become constant around 134 mmol/l. Neither sodium at birth nor peak sodium were different between male and female neonates.

Conclusions: Modeling and simulation allows to characterize individual serum sodium profiles and to identify risk factors in this vulnerable population. Consistent with immature regulation of sodium and water

balance, maximum fluctuation increases with decreasing gestational age. Interestingly, also delivery mode seems to have an impact on sodium peak concentration.

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II-77: *Catherine Sherwin* Tacrolimus population pharmacokinetics in paediatric kidney transplant patients

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Objectives: 1. To describe the pharmacokinetics (PK) of tacrolimus in paediatric kidney transplant recipients. 2. To determine the relationship between measures of tacrolimus exposure and renal function. 3. To determine if there were any differences in either the PK or pharmacodynamics (PD) of tacrolimus in brand versus generic formulations.

Methods: Data from 1999-2014 were extracted from the electronic medical records from Intermountain Healthcare network. Data were available on 95 paediatric patients with kidney transplant taking oral tacrolimus. Reliable data was available in 77 patients. Using the individual predicted PK parameters from the population model several exposure metrics were derived for each dosing interval including; Cmin, Cmax and partial AUCs (2, 4, 6, 8, 10, 12h). We investigated the relationship between tacrolimus exposure and creatinine clearance in the first 30 days post-transplantation, using a simple slope-intercept model as well as an Emax model.

Results: A total of 598 concentrations of tacrolimus were available for analysis. A one-compartment model described the final PK model, the significant covariates on clearance were haematocrit, body weight and post-transplant day. A total of 43 patients had data in the first 30 days post-transplant with a total of 470 creatinine concentrations available. The model that best described the relationship between tacrolimus exposure and creatinine clearance was an Emax model using a partial AUC of 4 hours. The significant covariates of this analysis were age, albumin, and formulation of the ED50 equivalent partial AUC 4h. The generic formulation (Sandoz) had a 35% increase partial AUC50 4h compared to the brand formulation.

Conclusions: In the present work we developed a population PK model for tacrolimus in pediatric kidney transplant recipients the significant covariates have been previously identified [1]. We also determined an exposure-response relationship between tacrolimus and creatinine clearance. This relationship was influenced by patients age and albumin concentrations. Furthermore, we show that there is a difference in the pharmacodynamic effects of tacrolimus when comparing the brand formulation to the generic.

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III-01: *Angela Äbelö* Population concentration-QT-modelling of CHF6001 following dry powder inhalation in healthy volunteers.

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Objectives:

CHF6001 is a potent and selective phosphodiesterase-4 (PDE-4) inhibitor currently under development for treatment of chronic obstructive pulmonary disease (COPD). CHF6001 is being developed for inhalation to help overcome the well-known gastrointestinal side effects associated with this therapeutic class when given orally [1]. Plasma concentrations and Fridericia corrected QT interval (QTcF) data from 2 phase I studies in healthy volunteers at different dose levels were used to assess potential QT prolongation liability. The exposure-response relationship was investigated using observed QtcF as well as placebo- and baseline corrected QTcF (ΔQTcF, ΔΔQTcF), respectively [2-4].

Methods:

CHF6001 plasma concentrations and QTcF data (12-lead ECGs extracted from 24-hour Holter recordings just before the scheduled blood sampling in triplicate) were obtained from 2 phase I, dose escalation studies: study FIH and study Extension. Both studies were double-blind, randomized, placebo-controlled and included a single ascending dose (SAD) part and a multiple ascending dose part (MAD). In the SAD part, across the two studies, single doses ranging from 20 to 4800 µg (leading to concentrations up to 2700 pg/mL) were administered via Aerolizer® (FIH) or NEXThaler® (Extension). In the MAD part of FIH study, doses ranging from 100 to 1600 µg (leading to concentrations up to 2000 pg/mL) were administered once daily via the Aerolizer® inhaler, while in the Extension study administration was twice daily in doses of 1200-2400 µg (up to 7000 pg/mL) via the NEXThaler® inhaler. The number of QTcF observations were 1310 (613 placebo) from 100 subjects. Three approaches were used in the modelling: **1)** using the observed QTcF measurements (mean of triplicate measurements) as dependent variable (DV), and estimation of baseline parameters including modeling of the circadian rhythm of QTcF over time, **2)** using the placebo adjusted change from baseline QTcF (ΔΔQTcF) as DV and **3)** using the change from baseline QTc (ΔQTcF) as DV. NONMEM V7.3.0 was used for all modelling.

Results:

1) Using only data from the subjects receiving placebo, a model describing the diurnal changes of QTcF was first developed. A function with three cosine terms described the data best. Next, using all data, a linear slope model was found to best describe the concentration-QTcF relationship. The slope was estimated at 0.19 (90% CI: -0.18 - 0.57) ms per fg/ml. **2)** A slope model performed the best also when ΔΔQTcF was used as DV. A slope of -0.23 (90% CI: -0.71 - 0.25) ms per fg/ml was estimated. **3)** A slope-intercept model was applied to the ΔQTcF data [3]. Time-after-dose, observed baseline QTcF and treatment (active/placebo) effects were added as covariates on the intercept. In addition, because of pooling 2 studies, a study effect was added on the residual error. A intercept of -1.09 (90% CI: -2.14 to -0.0485) ms was estimated. The corresponding slope was estimated at -0.58 (90% CI: -1.4 to -0.058) ms per fg/ml.

Simulations [5] with the model developed in **1)**, using uncertainty in the drug effect parameter, showed that the upper limit of the 90% CI of the mean QT-prolongation the mean QT-prolongation never exceeded 10 ms for concentrations up to 17500 pg/mL.

Conclusions:

The developed models adequately described the data of FIH and Extension studies, using QTcF, ΔΔQTcF and ΔQTcF as dependent variables. Similar slope estimates were obtained using the three approaches and in all cases the slope estimate was not significantly different from 0. Method **1)** gave the most precise estimate of slope (narrowest confidence interval). Given the available data, CHF6001 is unlikely to show an increase of QTcF of >10ms in the dose range studied.

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III-02: *Nada Abla Geiser* Development of PBPK drug models to support antimalarial combination strategy

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Introduction: In 2016, an estimated 216 million cases of malaria occurred worldwide, with an estimated 445 000 deaths. The current WHO recommendation for the treatment of uncomplicated falciparum malaria is artemisinin-based combination therapies (ACTs) [1]. Different ACTs are available and a better understanding of the pharmacokinetic behavior and potential interactions of each individual drug is needed in order to optimize the doses for new combinations of two or more drugs, and potentially adapt the doses in children, who receive sub-optimal doses in some cases [2].

Objectives: To develop PBPK models for the major antimalarial compounds currently in use and make them publicly available to researchers to support the development of new combinations, possibly including up to three antimalarials, and the dose optimization of existing combinations in children.

Methods: The following in vitro and physicochemical data were generated for all compounds at the Centre for Drug Candidate Optimisation, Monash University, Australia: Log D 7.4, pKa, apparent permeability and efflux ratio in Caco-2 cells, plasma protein binding, blood to plasma ratio, fraction unbound in microsomes, intrinsic clearance in human liver microsomes, aqueous solubility at pH 7.4, solubility in FaSSIF, FeSSIF and FaSSGF, direct CYP inhibition. CYP and UGT reaction phenotyping data were generated for selected compounds at Cyprotex when not available. These data were used as initial input parameters for building PBPK models for 16 marketed antimalarial drugs using Simcyp software (a Certara Company, Sheffield, UK). Available clinical data for these marketed compounds were included to further optimize the models. Victim and perpetrator properties of each compound were included based on in vitro data or pivotal drug-drug interaction studies, when available.

Results: Models were developed for 16 drugs: mefloquine, dihydroartesunate (DHA), lumefantrine, pyronaridine, primaquine (and its metabolite carboxyprimaquine), piperaquine, amodiaquine (and its metabolite desethylamodiaquine), atovaquone, proguanil (and its metabolite cycloguanil), artemether, chloroquine, azithromycin, doxycycline, pyrimethamine, quinine, and sulfadoxine. The model development followed the following workflow: an initial model was built using in vitro DMPK and physicochemical data, it was then evaluated and refined using clinical pharmacokinetic and drug-drug interaction data, when available, and finally verified using an independent clinical data set. Models may be applied as victim and perpetrator to understand drug-drug interaction potential via simulations, except models for atovaquone, azithromycin, lumefantrine, and pyrimethamine which can be used as perpetrators in DDI simulations only until information on elimination routes becomes available.

Conclusion: PBPK models for 16 antimalarial drugs are ready to be shared with researchers in the malaria field who are interested in using them for different applications. These models can be made available on request. This is the first step of an effort to develop open-source PBPK models for antimalarial compounds. The next step will focus on compounds in different stages of the research and development pipeline, to support the development of new combination therapies for malaria.

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III-03: *Amais Ahmad* Evaluation of Prediction Performance of In Silico PBPK models of oral drug absorption

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Introduction: Oral drug absorption is a complex process depending on many factors including the physiochemical properties of the drug, characteristics of the formulation and their interplay with dynamic gastrointestinal physiology. The ability to anticipate impact of these processes is of great importance in drug and formulation development in order to accurately predict the systemic exposure. *In silico* physiological-based pharmacokinetic (PBPK) models provides a systems pharmacology approach to predict plasma concentration-time profiles using *in vivo in vitro* extrapolation (IVIVE) and other preclinical data. Therefore, the models can help with various aspects of drug development process such as, for example, anticipation of human pharmacokinetics, choice of formulation, impact of physiology on exposure, prediction of sources of variability in exposure, formulation optimisation. Despite recent successes of PBPK in many areas of drug development, an improvement in their utility for evaluating oral absorption is much needed. Three PBPK software packages (GI-Sim, Simcyp®, and GastroPlus™) were evaluated as part of the Innovative medicine Initiative Oral Biopharmaceutics Tools (OrBiTo) project using "bottom-up" anticipation of human pharmacokinetics.

Objective: Evaluate the overall performance of PBPK software packages (GI-Sim, Simcyp®, and GastroPlus™)

Methods: Fifty eight active pharmaceutical ingredients (API) were chosen from an OrBiTo database, meeting the defined minimum inclusion criteria [1]. These 58 API represented over 200 human studies, and approximately 800 clinical study arms. Population representative simulations were performed by modellers from project partners. Input parameters were harmonised across different software packages by providing guidance on selection and calculation of input parameters. Pharmacokinetic (PK) parameters (AUC, C_{max}, T_{max}) of both simulated and clinical data were calculated using automated tools. Overall prediction performance was evaluated based on performance indicators (Fold error-FE, Average fold error-AFE and absolute average fold error-AAFE).

Results: On average, AUC value was over predicted with median FE of 1.57 and C_{max} was accurately predicted with median FE of 1.04. The prediction performance was fairly consistent across different software packages with a few exceptions mostly related to different input parameters for the models. Around half of the simulations were within 2-fold error for AUC and around 90% of the simulations were within 10-fold error for AUC. A general trend of overprediction was observed for all formulation with AFE ranging from 1.1 to 2.3 except slightly underprediction with immediate release (IR) suspensions with AFE of 0.9. There were higher percentages of within a certain specified fold errors in case of controlled release (CR) formulations as compared to IR formulations. Moreover, there was less FE variability in case of CR formulations, having AAFE approximately half than of IR formulations.

Conclusion: Average predictive performance did not seem related to software package but there was a very high level of variability in predictions for some APIs. This variability could be related to many factors

such as compound specific properties, the quality and availability of information, and errors in scaling from *in vitro* and preclinical *in vivo* data to human *in vivo* behaviour.

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III-04: *Jae Eun Ahn* Pharmacokinetic/Pharmacodynamic effects of PF-06648671, a novel gamma secretase modulator following single and multiple dose administration in healthy volunteers

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Objectives: Gamma secretase modulators **(**GSMs) shift the cleavage of amyloid-β (Aβ) peptides in favor of shorter forms (such as Aβ37 and Aβ38) without inhibiting overall amyloid precursor protein processing, thus preferentially lower the production of longer, amyloidogenic forms (Aβ42 and Aβ40). This study aimed to develop a population pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the differential effects of PF-06648671 on four Aβ species simultaneously. The developed model was intended to inform the dose selection for future studies.

Methods: Clinical PK/PD data were obtained from 133 healthy subjects in three Phase 1 studies. In the first-in-human single ascending dose study, PK data from 2, 4, 12, 40, 120, 240, 360 mg doses and placebo were obtained. From the single dose cerebrospinal fluid (CSF) biomarker study, PK as well as serial CSF samples were collected up to 36 hr post-dose (150, 300 mg doses, and placebo) by lumbar catheterization. In the multiple dose study, PK and PD samples were collected (40, 100, 200, 360 mg doses and placebo for 14 days) but only one post-baseline CSF sample was collected at trough, in addition to the baseline. A previously developed population PK model was used (2-compartment model with first-order absorption and elimination), fixing population PK parameters with PK data still included (PPP&D approach [1]). Drifts in baseline (a rising tendency) were observed in placebo subjects from the single dose biomarker study, which was empirically described in the PK/PD model. An indirect response model was implemented allowing PF-06648671 plasma concentrations to change the production rate of CSF Aβ peptides (decreased Aβ42 and Aβ40; increased Aβ37 and Aβ38). Simple inhibitory Emax (Imax) and sigmoidal Emax models were applied for longer and shorter forms of Aβ, respectively. Baseline correlation among Aβ species was also accounted for in the model. NONMEM 7.3 [2] was used for population PK/PD modeling.

Results: The PK/PD model described the observed Aβ responses from both single and multiple dose studies reasonably well. The inhibitory effect on CSF Aβ42 was estimated to be greater than on Aβ40 (Imax and IC50: 0.744 and 421 ng/mL for Aβ42 vs. 0.725 and 1228 ng/mL for Aβ40) whereas the stimulatory effect on Aβ37 was greater than on Aβ38 (Emax and EC50: 5.63 and 1285 ng/mL for Aβ37 vs. 0.869 and 1765 ng/mL for Aβ38). Precision of the parameter estimates was reasonable (relative standard errors, RSEs, were less than 40 %) except for Aβ38, for which a step-like response was observed. The PK/PD model suggested CSF Aβ42 average reductions from baseline at steady state of approximately 50%, 59, and 65%, after 75, 150, and 300 mg q.d. administrations respectively. The reductions in ratios of Aβ42 to shorter peptides (Aβ42: Aβ40, Aβ42: Aβ38, and Aβ42: Aβ37) were predicted to reach a plateau after a daily dose of approximately 150 mg.

Conclusions: An indirect response model was developed to characterize differential and exposure-dependent effects of PF-06648671 on CSF Aβ peptides in healthy subjects. The PK/PD model was used to predict the drug effect on individual Aβ peptides as well as the ratio of Aβ peptides in CSF across a range of PF-06648671 doses. The model-predicted changes in CSF concentrations of different Aβ species and ratios of long to short fragments were in keeping with the expected pharmacological actions of a GSM. The results of this effort have utility in informing dose selection for potential future clinical trials of PF-06648671.

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III-05: *Yasunori Aoki* Second order Taylor expansion of likelihood-based models for fast covariate and random effect model building

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Objectives:

Linearization of models with respect to the random effect variable has been proved to work well for continuous models and the FOCE(I) approximation [1]. The approach enables fast and sometimes more stable estimation of covariate and random effects models, once as a structural model has been identified. However, for likelihood-based models, first order mean and variance linearization is not feasible since the data are not implicitly assumed normally distributed. Instead, a second order Taylor expansion is needed. The aim of this work is to implement a second order Taylor expansion to improve speed and stability for likelihood-based models.

Methods:

The -2 log likelihood of the individual observation is approximated with second-order Taylor series expansion at the empirical Bayes estimate (EBE). The gradient vector and Hessian matrix required for this expansion are calculated using e.g. numerical differentiation of the individual log likelihood with respect to the EBEs (e.g., in NONMEM these values can be obtained as G(,) in verbatim code). The key motivation for this approach is that, since Laplace approximation uses the second order approximation of the log likelihood when using Laplace approximation, the above approach does not influence the final outcome of the likelihood calculation.

Once the approximate model is constructed, it can be modified to add and test covariate relationships or change the random effects. The key advantage of this approximation is that it does not require any additional computation of the structural model predictions. Hence extensive explorations of various functions for the covariates and random effects models become feasible, in fact using an analytical quadratic approximation, even for models with long computation time, e.g. for differential equations models. This methodology was tested using the following different models:

- pharmacokinetics model of Phénobarbital (PHENO) [2]
- pharmacokinetics model of Phénobarbital with lower limit of quantification treatment using M3 method (PHENO with M3) [2]
- minimal continuous-time Markov model for the Likert pain score (mCTMM) [3]
- first-order Markov model for adverse reactions (Fatigue) experienced by Sunitinib-treated patients (MARKOV) [4]
- bounded integer model for ADAS-cog score (BI) [5,6]

For MARKOV and BI, we have conducted extensive covariate search using the SCM method implemented in PsN [7,8].

Results:

The comparison of the computed -2 log likelihood (OFV) and computation time of the final model are tabulated below. (original model/approximated model using proposed method)

PHENO:	867.61 / 868.31	0.02 sec / 0.01 sec
PHENO with M3:	818.18 / 817.63	0.02 sec / 0.01 sec
mCTMM:	48902.16 / 48900.61	526 sec / 0.02 sec
MARKOV (base model):	6765.61 / 6763.99	3632sec / 59 sec
MARKOV (SCM):	6765.61 / 6763.99	9512.95 sec / 697.38 sec
BI (base model):	28122.99 / 28122.99	76.07 sec / 1.49 sec
BI (SCM):	27569.13 / 27569.10	14099.83 sec / 168.08 sec

As can be seen from the above table, some approximation error can be observed (e.g., OFV difference of 1.62 for MARKOV); however, a significant speed up in the computation was achieved (e.g., 4hr to 3min for SCM of BI).

For MARKOV, the SCM did not find any statistically significant covariates. For BI, the baseline Minimum Mental State Examination score was significant covariates for both baseline ADAS-cog score and disease progression. Both of these results were consistent between the original model and approximated model while it was significantly faster to run SCM using approximated model.

Conclusions:

A strategy to implement second-order Taylor expansion of the likelihood of the nonlinear mixed effect model was derived, which enables fast and stable assessments of covariates for likelihood-based models. The proposed method expands the use of the linearization technique [1,7,9] to also include likelihood-based models.

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III-06: *Usman Arshad* Development of visual predictive checks accounting for multimodal parameter distributions in mixture models

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Objective: The underlying basic assumption of interindividual variability being unimodally distributed in nonlinear mixed effects models does not hold when the studied population exhibits multimodal parameter distributions (e.g. fast or slow metabolizers). Multimodal distributions can either be described by a covariate or with the implementation of mixture models which allow the identification of parameters specific to a subpopulation. Despite their utility to describe data arising from a population with underlying heterogeneity, there are limitations in assessing mixture models, since the common assessment tools do not account for the multimodality in parameter distributions. Visual predictive checks (VPCs) are a standard simulation based diagnostics tools, but these are not yet adapted for the mixture models. The aim of this project was to design VPCs accounting for multimodal parameter distributions and thereby allow (i) the diagnosis of the mixture component aspects of the model, and (ii) more powerful assessment of other model components by reducing between-subpopulation variability from the graphs.

Methods: Analysis with mixture models provides two individual-level metrics of subpopulation association (i) the probability for an individual to belong to subpopulation[1], and (ii) the most likely subpopulation for an individual to belong to. The former metric is in the NONMEM program termed PMIX and can be retrieved from the *.phm file which is a standard output of models with mixture components. The latter metric is retrievable as the MIXEST variable and can be output to standard table files. Naturally, MIXEST can also be easily calculated from the PMIX information. VPCs are based on a comparison of simulated and observed data statistics. In order to retrieve individual PMIX and MIXEST information for simulated data, an evaluation (or estimation) step is necessary.

Mixture model specific VPCs were developed based on the output from PsN and implemented in Xpose/R. The mixture-specific VPCs were developed and assessed using both simulated data. For illustration, the approaches were also applied to an irinotecan mixture model[2] demonstrating 30% lower clearance of irinotecan metabolite (SN-38) in individuals with UGT1A1 homo/hetero vs wild-type genotype. The irinotecan/SN-38 model was applied to an external data set[3] and diagnostics were generated.

Results: Two types of mixture model specific VPCs were developed and implemented. The first type splits the observed and simulated data according to the MIXEST assignment. Thus the most likely subpopulation for each real or simulated individual is estimated and directing the VPC panel to which the data is allocated. As the individual subpopulation allocation frequency can differ between real and simulation data, and because such an allocation difference can be a sign of model misspecification, these numbers are included in the graphical display. A shortcoming of the MIXEST-based allocation strategy is that there is a tendency for subjects to be allocated to the dominating subpopulation (similar to the shrinkage phenomenon in individual, empirical Bayes, parameter estimation). This shortcoming can be avoided through the second type of VPC which splits observed and simulated data according to the PMIX value. VPCs with segregated subpopulations were helpful in identifying model misspecifications in case of irinotecan mixture model which were not evident with standard normal VPCs previously. It was evidenced that the model was over-predictive for fast metabolizers while under-predictive in case of slow metabolizers.

Conclusions: A graphical and statistical comparison of observations and predictions derived from the multimodal distributions in mixture models is presented. Partitioning of observed and predicted data between subpopulations can be done in two ways depending upon the underlying information (MIXEST or PMIX). These approaches can be a useful diagnostic tool for the development and evaluation of mixture models in future.

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III-07: *Muhammad Waqar Ashraf* A semi-PBPK model to describe the mechanism based drug-drug interaction between S-ketamine and ticlopidine in healthy human volunteers.

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Objectives:

Low dose *S*-Ketamine has been shown to be useful as an adjuvant in pain medicine (1). However oral *S*-ketamine has a low bioavailability and cytochrome P450 inhibitors can significantly change the exposure of *S*-ketamine, as demonstrated by *in-vitro* (2) and *in-vivo* studies (3). Ticlopidine is a mechanism-based inhibitor of CYP2B6, the enzyme responsible (≥60%) for the metabolism of *S*-ketamine to *S*-norketamine in humans (2). Simultaneous use can, therefore, increase S-ketamine drug concentrations and exposure and may cause problems in pain therapy. Accurate prediction of the drug-drug interaction (DDI) between these two drugs can help to devise precise dosing schemes of *S*-ketamine for pain relief. The objectives of this study are 1) Development of a physiologically based pharmacokinetic model to characterize the complex pharmacokinetics (PK) of orally administered *S*-ketamine, its primary metabolite *S*-norketamine, and ticlopidine 2) Development of DDI model to account for the dynamic mechanism based interaction between *S*-Ketamine and Ticlopidine.

Methods:

S-ketamine, *S*-norketamine, and ticlopidine data were gathered from five randomized, placebo-controlled, crossover studies (3-7). Nonlinear mixed effects modeling was performed with NONMEM software (version 7.3.0), and Perl-Speaks-NONMEM (PsN) and R based scripts were used for model coordination and evaluation. A semi-mechanistic structural model was developed with differential equations for gut-wall, portal vein, and liver, alongside a two (ticlopidine and *S*-norketamine) or three (*S*-ketamine) compartmental mammillary model. Well-stirred clearance models were used to describe first pass in the gut-wall and liver metabolism. After developing functional models for each drug, a DDI model based on Palacharla et al. 2017 (2) was developed using *S*-ketamine concentration-time data from individuals who had undergone a 6-day ticlopidine pre-dosing (7). The equations used for specifying DDI model used a competitive as well as a non-competitive component. It was assumed that ticlopidine pre-dosing completely abolishes CYP2B6 functionality, which permitted us to change the extent of CYP2B6 inhibition dynamically using DDI model equations (≥60%), in favor of an adequate model fit (2). Constants required for calculating variables of DDI model were obtained directly from the literature (ticlopidine KI = 0.57 µM (8), ticlopidine KINACT = 18/hr (8), S-ketamine fraction metabolized by CYP2B6 = 0.60 (2), physiological degradation rate of CYP2B6 = 0.022/hr (8), Ticlopidine IC50 CYP2B6 = 0.04 µM (10)). Additionally, an exponential between-subject-variability (BSV) and a proportional residual variability (RV) model was used in the final model for all three substances.

Results:

The semi-mechanistic PBPK model described adequately the pharmacokinetics of *S*-ketamine, *S*-norketamine and ticlopidine, as demonstrated by plausible parameter estimates and standard goodness-of-fit (GOF) plots. Our modeling results indicate that, 1) first order absorption rate constants were adequate to account for the absorption of *S*-ketamine and ticlopidine (ketKA = 1.71 /hr (%RSE = 17.5%), tclKA = 3.3 /hr (fixed), 2) gutwall clearance, plays a minor role in the metabolism of S-ketamine and ticlopidine (i.e. ketCLint,gw = 0.07 L/hr (42%), tclCLint,gw = 0 L/hr (fixed) in comparison to liver (ketCLint.h = 312 L/hr (14%), norkCLint,h = 74 L/hr (8%), tclCLint,h = 261 L/hr (154%)), 3) A three compartment model (V1 = 15.5 L (40%), CL1 = 297 L (11%), V2 = 101 L (9%), CL2 = 22.6 L (6%), V3 = 183 L (4%)) adequately described *S*-ketamine disposition kinetics, while a two compartmental model was implemented for *S*-norketamine (V1 = 85.3 L (5%), CL1 = 21 L (11.7%), V2 = 87.7 L (8.3%)) and Ticlopidine (V1 = 95.4 L (42%), CL1 = 30.1 L (30%), V2 = 5193 L (61%)). 4) Finally, the DDI model could adequately harness the complex mechanism based DDI between ticlopidine and *S*-ketamine. A 70% inhibition of *S*-ketamine clearance (signifying that the fraction of *S*-ketamine metabolized by CYP2B6 = 0.70) resulted in a good model fit. The final model was further evaluated with prediction-corrected visual predictive checks and normalized prediction distribution errors, both of which proved the appropriateness of the final model.

Conclusions:

The semi-mechanistic DDI model developed in the study adequately describes S-ketamine, S-norketamine and ticlopidine pharmacokinetic data and inter-individual variability in healthy human volunteers, and also accounts for the dynamic DDI between *S*-ketamine and ticlopidine.

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III-08: *Magnus Åstrand* Longitudinal pharmacometric modelling of serum potassium lowering effect of sodium zirconium cyclosilicate in patients with hyperkalemia

Magnus Åstrand, Mats Någård, David W. Boulton, Bengt Hamrén

Objectives: Sodium zirconium cyclosilicate (SZC, LOKELMA™) is an orally administered non-absorbed treatment for hyperkalaemia, acting locally in the gastrointestinal tract by exchange of potassium for hydrogen and sodium. An exploratory modelling and simulation exercise has been undertaken to evaluate the serum potassium concentration (S-K) lowering effect of SZC in patients with hyperkalemia (S-K value >5 mmol/L). The objective was to characterize the relationship between S-K lowering response and SZC dose for the correction and maintenance treatment phases across multiple studies. The modelling included data from 3 Phase 2/3 studies and comprised of the following main steps:
i) Build a longitudinal pharmacodynamic model to describe the time course of S-K using all available data on S-K and administered doses of SZC
ii) Describe the S-K lowering dose response of SZC for correction (three time daily [TID]) and maintenance phases (once daily [OD])
iii) Identify and quantify the influence of baseline covariates on both the SZC-induced S-K lowering effect and placebo response

Methods: A longitudinal model describing the S-K vs SZC dose and time was built using data from a total of 1101 patients with hyperkalemia. The mean(SD) S-K at baseline was 5.38(0.39) mmol/L. The S-K over time was described by an indirect response model. A virtual pharmacokinetic-pharmacodynamic model (PK-PD) modelling approach was used by introducing a drug exposure component although there was no data on drug exposure measured. The level and duration of this virtual exposure was determined by the amount and frequency of SZC doses and an elimination rate parameter in line with a more standard PK-PD model. Introducing the virtual exposure enabled describing the dose response for both TID and OD dosing during the correction and maintenance phase respectively. Thus, the modelling included a virtual SZC exposure component and the S-K lowering effect was then described using the virtual exposure via a sigmoid exposure-response model. The influence of baseline covariates was explored for both the SZC-induced S-K lowering (concentration at half maximum effect [EC50]), the placebo response and the rate of change of S-K.

Results: The developed model was overall consistent with the included S-K data, as demonstrated by model diagnostics, and adequate for the purpose of predicting S-K changes from baseline. A sigmoid Emax exposure response was used in the modelling. The modelling found a high value for the EC50 parameter and a hill coefficient of 1.3. Within the range of SZC doses studied, the predicted dose-response was therefore close to linear. The predicted (with 95% confidence interval [CI]) placebo-adjusted S-K change from baseline after 48 hours TID correction phase treatment was -0.26 (-0.29 to -0.23) mmol/L for 5 g SZC, and -0.53 (-0.59 to -0.48) mmol/L for the 10 g SZC dose. The predicted (with 95% CI) placebo adjusted S-K change from baseline for 28 days OD maintenance treatment was -0.25 (-0.28 to -0.22) mmol/L for 5 g SZC, -0.52 (-0.58 to -0.45) mmol/L for 10 g SZC, and -0.75 (-0.85 to -0.65) mmol/L for the 15 g SZC dose. The forward and backward covariate selection step identified a total of 9 covariates, 5 for EC50, 3 for the placebo effect and 1 for the S-K dynamics (Kout). Greater treatment response was associated with high S-K baseline, older patients, lower body weight and lower eGFR. Greater treatment response was also predicted for Black or African American compared to White.

Conclusions: The dose response for both TID correction at doses 0 to 10g, and OD maintenance treatment at doses 0 to 15g is close to linear. A total of 9 covariates were identified. However, the placebo corrected change from baseline following 10g TID dosing for 48 hours for all covariates were within the range -0.75 to -0.39 mmol/L, supporting using the same SZC dose recommendation for all patients in the pooled study population.

III-09: *Linda Aulin* Quantitative modelling of procalcitonin as a treatment response biomarker in sepsis

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Introduction:

The use of host response biomarkers to guide antibiotic treatment of bacterial infections is well established. Procalcitonin (PCT) represents a biomarker with favorable properties, including specificity to bacterial infections, rapid induction and short half-life compared to C-reactive protein[1]. Previously, PCT has been shown to allow early stopping of antibiotics without impacting clinical outcomes in sepsis patients[2].

Sepsis is a condition characterized by a dysregulated immune response to infections, which leads to organ and tissue damage and is associated with a high mortality[3]. To this end, broad-coverage AB treatment consisting of multiple combinations is typically used. Biomarkers to quantify the effect of such combinations may be relevant for treatment optimization. We hypothesized that characterization of PCT and its kinetics may be valuable to predict clinical outcomes and as a surrogate biomarker to quantify individual treatment response.

Objectives:

We aimed to evaluate early PCT as a predictor for 28-day survival and to quantitatively characterize the kinetics of PCT to assess the effect of antibiotic combination treatments in a cohort of sepsis patients.

Methods:

Study data: Data from a previously conducted randomized controlled trial investigating PCT to guide early treatment discontinuation was used (www.clinicaltrials.gov, NCT01139489). Data for 1546 patients was available with a total of 4928 PCT values (median: 6 PCT values/patient in PCT arm). Antibiotic treatments comprised of antibiotic mono- or combination therapies, with a median of 2 antibiotics used alone or in combination per patient (range: 1-7 antibiotics/patient).

Clinical outcome analysis: A parametric proportional hazard survival model was developed to describe overall 28-day survival evaluating several probability distributions to describe the baseline hazard. A univariate analysis was conducted to identify early PCT predictors of survival.

PCT kinetic model: A dynamical mixed effect model was developed to quantitatively characterize the kinetics of PCT in septic patients during and after antibiotic treatment. Unique treatments were defined based on classification at drug class level. A random effect was used to model inter-treatment variability (ITV).

Combination treatment analysis: ITVs were used to quantify individual treatment response. ITVs were analyzed using linear regression with regression coefficients for individual antibiotics present in the

combination, assuming additivity. The resulting regression coefficients were used to compute pairwise expected antibiotic treatment effects. Residuals between predicted and observed treatment effect were computed in order to identify deviations from additivity.

Results:

Clinical outcome analysis: A Gompertz distribution best described overall 28-day survival. PCT was found to be a significant predictor of 28-day survival, with the absolute PCT value at day 2 being the earliest predictor (β: 3.7 x 10^{-3}, range: 0-400 µg/L).

PCT kinetic model: A structural model with a first-order growth or degradation of PCT (k_{PCT}) was used, and further included terms for the baseline PCT (PCT_0), a delay term (PCT_{delay}), and a random effect term (ITV_{PCT}) to quantify treatment associated changes in PCT kinetics within a patient. Parameter estimates were: PCT_0 1.52 µg/L (RSE 9%, IIV 218.6%), k_{PCT} 0.278 day^{-1} (RSE 6%), PCT_{delay} 1.85 (RSE 6%), and ITV_{PCT} estimated at a variance of 1.34 (RSE 26%).

Combination treatment analysis: antibiotic-specific treatment response regression coefficients ranged between -0.755 and 0.352 indicating associations of both positive and negative PCT kinetics. For several pairs we observed trends suggesting synergy or antagonism.

Conclusions:

We quantitatively characterized PCT and its kinetics in a large cohort of sepsis patients using time-to-event and mixed-effect modelling to obtain insight into antibiotic treatment response. This approach could potentially be generalized to other bacterial infections and host biomarkers.

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III-10: *Geraldine Ayral* Development of guidelines to efficiently choose and diagnose target-mediated drug disposition models

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Objectives: The use of target-mediated drug disposition (TMDD) models is growing at the same time as the number of biologic drugs in development. A large variety of TMDD models have been proposed in the literature, corresponding to different modeling assumptions [1,2]. Yet, it is often difficult to decide which TMDD approximation is the most appropriate for a given data set. In addition, the long runtime of TMDD models imposes an efficient model testing strategy. In this poster, we present guidelines to choose an appropriate model in a minimal number of iterations, using both a priori information and a posteriori diagnostic plots.

Methods: To identify a priori information that is relevant to TMDD model choice, we simulate the most common TMDD models, which are available in the TMDD model library of the MonolixSuite2018R1. The profiles obtained with different parameter values are compared.

To identify a posteriori information, several data sets have been simulated from the different TMDD models, using different parameter values within the physiological range. Several realistic limits of quantification values have also been tried. The fit of wrong and correct models to the simulated data permits to identify the most informative diagnostic plots and how to interpret the observed patterns.

Results: A priori information can be used to reduce the choice of TMDD approximations, such as binding rate and/or dissociation constants obtained from Biacore experiments. We simulate and plot the typical concentration-time curve of typical values of the ligand-receptor binding and identify threshold values for which the full/quasi-equilibrium models and the full/irreversible-binding models are indistinguishable. In those cases, the full model would be not identifiable.

Next, we performed a sensitivity analysis of each of the TMDD approximations. By comparing the range of concentrations recorded in the data set with the concentration-time curve's zones where the parameters have an influence, non-identifiable parameters can be identified. These parameters can either be fixed to physiologically meaningful values or a model with less parameters can be chosen. The range of doses used in the data set can also influence the choice of a model. Indeed, if the initial ligand concentration is much smaller than the initial receptor concentration, the initial free ligand concentration drop (due to the binding of the ligand to the receptor) will not be observable. As a result, the parameter characterizing the receptor concentration will not be identifiable.

Finally, we fit each TMDD model to the simulated data sets in order to identify key patterns indicating a model misspecification. The following plots have been found especially informative:

- Residuals (individual weighted residuals and NPDE): trends in the residuals are often visible when an underparameterized model is used. Residuals give information about the time and concentration range where the model lacks flexibility. Combined with the parameter sensitivity analysis, the user can easily see which model could be more appropriate.

- Individual parameters versus dose covariate: the individual parameter distributions can be stratified by dose groups. If the distributions show significant trends with respect to increasing doses, the model is misspecified and a more complex model should be tried.
- Condition number and correlation matrix of the estimates: high correlations between parameters indicate that the parameters have the same (or opposite) influence on the predictions. Using an interactive simulation application such as Mlxplore, the information from the correlation matrix can be verified and visually grasped to guide the choice of another model.

Conclusion: With the development of TMDD model libraries, the testing of several TMDD models to model a data set has been simplified. Yet choosing a first model and interpreting the diagnostic plots and results to arrive at a satisfactory model is still challenging. Using a combination of model simulations, parameter sensitivity analysis and fits on simulated data, we have developed guidelines to efficiently choose and diagnose TMDD models.

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III-11: *Vanessa Baier* Developing a physiology-based model of bile acid metabolism in men

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Objectives: Drug-induced liver injuries (DILI) are a frequent reason for safety-related project closure of pharmaceutical development programs as their mechanisms are unclear and they are often unidentifiable in standard preclinical tests [1]. Cholestasis, the state of impaired bile secretion, is a common clinical manifestation of DILI. Dedicated computational models would be useful for prior identification of potential aberrant states of bile acid metabolism and a subsequent early identification of compounds with cholestatic risk. As bile acids undergo extensive enterohepatic cycling and are distributed on a whole-body scale, a systemic model at organism level is needed to truly understand the occurrence of cholestasis. Our objectives are 1) to develop a PB model of bile acid metabolism in healthy men, 2) to quantify the effects of different phenotypes on bile acid metabolism, and 3) to predict drug-induced cholestasis.

Methods: The developed bile acid model (BAM) was structurally derived from the physiology-based pharmacokinetic (PBPK) model implemented in PKSim® (Open Systems Pharmacology Suite, version 7.2) [2, 3]. Processes essential for bile acid metabolism such as biosynthesis, excretion, and active transports were identified by comprehensive literature research and were included in the model [3–5]. Additionally, gallbladder emptying following meal intake was considered. So far, one exemplary bile acid – glycochenodeoxycholic acid - was used as a surrogate bile acid for the total pool. Parameter estimation was performed by fitting the model to bile acid concentration-time profiles in blood reported in literature [6–8].

Results: The developed whole-body physiology-based BAM describes the bile acid metabolism in a healthy reference individual. The model was validated with literature values for bile acid plasma levels at steady state as well as dynamic changes following ingestion of three meals per day and consequent gallbladder emptying. The model allows simulation of bile acid concentrations in tissue compartments such as the intracellular space of the liver which is of particular relevance to mechanistically assess occurrence of cholestasis. Based on the healthy reference model, two different impairments of the bile salt export pump (BSEP) were simulated. First, the simulation of genetic defects in BSEP like Benign Recurrent Intrahepatic Cholestasis (BRIC) type 2 [9] points to slightly increased bile acid concentrations (3% and 15% in venous blood and liver cells, respectively) in these individuals. Our model therefore suggests a special susceptibility of this phenotype towards occurrence of DILI. In a second *in silico* study, effects of Cyclosporine A (CsA) on bile acid metabolism were predicted by combining the BAM with a PBPK model of CsA [10] and *in vitro* inhibitory data [11]. Simulations of a twice daily CsA administration revealed more pronounced effects in BRIC patients than in healthy individuals with increased bile acid concentrations of 6% vs. 3.5% and 41% vs. 23% in venous blood and liver cells, respectively. Taken together, the simulated scenarios are a first step towards an *in silico* risk assessment for drug-induced cholestasis.

Conclusion: The physiology-based model of bile acid metabolism describes the circulation of bile acids within the human body at organism level. It was initially validated for a healthy reference state and subsequently used to investigate aberrant states of bile acid metabolism such as drug-induced cholestasis. Straightforward integration of *in vitro* data, for example describing changes in ADME gene expression (ADME: absorption, distribution, metabolism and excretion), allows predictions about drug-induced effects on bile acid metabolism. Next, we will integrate high-quality time-resolved omics data gathered within the

HeCaToS project to enhance the models significance [12]. The model can support the early identification of drug-induced cholestasis to avoid project closure at late phases of clinical development as well as to increase patient safety in general.

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III-12: *Pavel Balazki* A Physiologically-based Quantitative Systems Pharmacology model of the incretin hormones GLP-1 and GIP

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Objectives:

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are crucial for the regulation of postprandial glucose. Their therapeutic effects are mainly achieved by potentiation of insulin secretion (GLP-1 and GIP) and by slowing down the gastric emptying rate (GLP-1) [1]. Most of the available data on concentrations of GLP-1 and GIP do not distinguish between the intact forms of the peptides and their primary metabolites due the use of non-specific assays, and only few sources report the concentrations of the biologically active forms. Our objective is to develop a physiologically-based (PB) model of metabolization and secretion of the two hormones that accounts for the pharmacokinetics (PK) of both, parent and metabolite of the two peptides.

Methods:

The PBPK models for GLP-1 and GIP were developed with PK-Sim® and MoBi® as part of the Open Systems Pharmacology Suite (OSPS), version 7.2 [2]. An extensive literature research was performed to identify the processes involved in the metabolism of GLP-1 and GIP [excerpt: 1,3–5]. Mean model parameters were estimated by fitting simulation results to concentration-time profiles of intact GLP-1 and GIP, their primary metabolites, and/or “total peptide”.

Data used for characterization of degradation and elimination processes include incubation of human plasma with GLP-1 and/or GIP [6–8], bolus injections [9,10], and continuous intravenous infusions of the peptides. Contribution of kidneys to the total elimination of GLP-1, GIP, and their primary metabolites, was estimated with the datasets reported by Idorn *et al.* [11] and Asmar *et al.* [12,13] and Albrechtsen *et al.* [14].

Parameters governing the secretion of the hormones were estimated by fitting the model to data from intraduodenal infusions of glucose [15–17].

Results:

The model includes degradation of the active hormones by the enzyme dipeptidyl-peptidase 4 (DPP-4), glomerular filtration, and active secretion into renal tubulus. Degradation of the peptides occurs in tissue’s interstitial space through membrane-located DPP-4, and in plasma through free-floating and endothelium-located DPP-4. The primary metabolites are eliminated via tubular secretion and degradation by the enzyme neutral endopeptidase (NEP, also known as membrane metallo-endopeptidase, MME).

GLP-1 is secreted from the L-Cells located in mucosa of ileum and colon. The basal secretion rate is enhanced by oral glucose load in a biphasic nature. The first phase is dependent on the concentration of glucose in the duodenum, the second phase is coupled to glucose uptake through sodium-glucose co-transporter 1 (SGLT1) in the direct proximity of the L-Cells.

Secretion of GIP is implemented in the duodenum and jejunum and is coupled to SGLT1-mediated glucose uptake in the respective region.

The model successfully mimics the complex behavior of incretin secretion and degradation while being consistent with reported concentrations of intact hormones and their primary metabolites. The expression of endothelial DPP-4 was identified as the most important factor to describe highly variable data from all 28 sources gathered for model assessment.

Conclusions:

We here present the first PB model of the two most important incretin hormones including both, the intact forms and their primary metabolites. The advantage of such a model is that it can reproduce the majority of reported data on incretin concentrations, regardless of the applied assays, e.g., the model could be used to estimate the concentration of intact peptides from "total" concentration data. In a next step, the model will be integrated into the physiologically based pharmacokinetics and pharmacodynamics (PBPK/PD) Quantitative Systems Pharmacology (QSP) Diabetes Platform [18,19] to couple the PK to the PD on gastric emptying, glucose metabolism and insulin and glucagon secretion.

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III-13: *Belén Pérez Solans* Mechanistic model of the myeloablative effects of treosulfan and busulfan in pediatric patients undergoing bone marrow transplant

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Introduction: Hematopoietic Stem Cell Transplantation (HSCT) is a procedure where healthy donor cells are infused to a recipient with the intention of replacing the haematopoietic system in total or in part [1], being one of the most common treatments of a wide range of malignant and non-malignant disorders in children [2]. Prior to HSCT, the ablation of the host immune system is achieved by administering conditioning drugs and/or total body irradiation. There is currently a debate surrounding the relative merits of busulfan (Bu) and treosulfan (Treo), which are used to deplete myeloid cells prior to transplantation. Identifying patient characteristics associated with the dynamics of myeloid reconstitution (inferred from neutrophils) and predicting individual trajectories may prove to be useful in understanding post-HSCT recovery. To do that, pharmacokinetic/pharmacodynamic (PKPD) models were developed, in which both the rate and extent of reconstitution can be obtained by deriving the dynamics of cell count over time.

Objectives: The **objectives** of the study were (i) to build a joint mechanistic PKPD model of neutrophil count over time and establish a relationship with Bu and Treo plasma concentrations, (ii) compare the myeloablative effects of Bu and Treo in the shape of the PD effect curve and (iii) identify patient characteristics associated with the inter-individual variability in myeloid cell dynamics.

Methods: In this retrospective single-center study, blood concentrations of Bu were quantified in samples acquired for routine drug therapeutic monitoring (TDM). The PK characteristics of Treo were obtained from a model developed as part of a previous study [manuscript under preparation], and PK predicted for those patients without measured concentrations. Daily neutrophil count data from the start of drug administration until 3 months post-transplant was also available from electronic health records. In total 11,555 observations from 152 paediatric patients (median post menstrual age in weeks (PMAW) 204.14, ranging from 47.71 to 948.57 weeks), 85 receiving Bu (median PMAW 216.29, range 69.57 – 948.57 PMAW) and 67 receiving Treo (median PMAW 122.14, range 47.71 – 879.86 PMAW) were included. Integrating all the available data, a PK/PD model was built NONMEM 7.3. The analysis was performed simultaneously for both drugs.

Results: a joint mechanistic PKPD model of neutrophil count over time for Bu and Treo was successfully developed. The blood concentration vs time profiles of Bu and Treo were described by a two-compartment model for both drugs. The drug effects were modelled using an EMAX model for both of the drugs, which resulted significantly better ($p<0.01$) than a linear model. System parameters (steady-state neutrophil count after transplant (CIRC0), mean transit time (MTT) and feedback parameter (GAMMA)) were consistent across drugs and were therefore the same for Bu and Treo, being the estimates 1.06, 5.74 days and 0.114. Inter-Individual Variability (IIV) could be estimated for all of parameters, being 54.2, 24.5 and 48.2% for CIRC0, MTT and GAMMA, respectively. Since patients may not enter the study at steady-state and/or the post transplant steady-state level may have a different homeostatic set point than the baseline, a different steady state of neutrophils was estimated after transplant than the baseline. The main differences between patients receiving different drugs was the baseline neutrophil value (5.08 for Bu patients vs 1.62 for Treo patients). The myeloablative effects of Treo were steeper and produced earlier in

time than those of Bu (EMAX = 2.47 vs 0.57 for Treo and Bu, respectively). A covariate analysis did not find other significant predictors of response.

Conclusions: Drug exposure to the main myeloablative conditioning drugs given to paediatric patients receiving HSCT was successfully described by a two compartment model for each of the drugs, and was linked to neutrophil count dynamics over time and recovery through mixed-effects modelling, and thus, a joint mechanistic PKPD model was built. Further work will now seek to link early neutrophil dynamics to long-term myeloid recovery measured through chimerism analysis.

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III-14: *Irina Baltcheva* Model-based dose selection for the Phase 2b study of ianalumab in primary Sjögren's Syndrome

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Objectives:

Ianalumab is a novel human monoclonal antibody (mAb) that binds to the B-cell Activating Factor receptor (BAFFr). It has a dual mode of action *in vivo*: (i) rapid and profound B-cell depletion via antibody-dependent cell-mediated cytotoxicity (ADCC) and (ii) blockade of the BAFF-BAFFr signaling of tissue-residing activated B cells. A dose range finding Phase 2b study in primary Sjögren Syndrome (pSS) patients is currently ongoing (NCT02962895). The objective of the PKPD modeling presented here was to support the selection of ianalumab dose levels and regimens to be tested in the above Phase 2b study considering both mechanisms of action. A population PKPD model for circulating B cells based on clinical data had been established previously. To account for the second mode of action for which data was not available, a hypothesis-driven model of tissue receptor occupancy (RO) had to be developed. Both models were used to support dose selection and this model-based approach was approved by Health Authorities.

Methods:

We used a modeling approach to establish the dose-exposure-response relationship for both biomarkers related to the compound's mode of action: 1) circulating B cells and 2) BAFF receptor occupancy (RO) by ianalumab in a disease-related tissue. A PKPD model for the first biomarker was available, based on data from Rheumatoid Arthritis (RA) and pSS patients. The population PK model had two compartments with linear clearance. B cell dynamics were represented by a turnover model with a peripheral compartment. Serum drug concentration was assumed to exert an indirect effect on circulating B cells by stimulating their death rate. No data was available for the second biomarker; we therefore used a model to predict RO in a hypothetical disease-related tissue. The RO model links the serum concentration to the unmeasured tissue RO using a simple analytical expression that represents the competitive binding between ianalumab and soluble BAFF (sBAFF) on BAFFr under quasi-steady state conditions [1].

Results:

Simulations based on the above PKPD models supported the selection of three dose levels to be tested in the Phase 2b study in pSS patients. The "low" dose is expected to provide exposures that just lead to depletion of B cells in the systemic circulation. The "high" dose was selected to approximately match the exposure in the proof-of-concept (PoC) trial that demonstrated efficacy in pSS patients [2]. The "medium" dose was chosen to provide a good spread of exposures between the "high" and the "low" doses. It is intended to provide evidence of increased efficacy due to targeting the BAFFr pathway, in addition to the expected clinical benefit due to complete depletion of circulating B cells. This dose is needed to describe a full dose-exposure-response model in pSS patients.

Conclusions:

We present a model-based approach to Phase 2b dose selection which includes data- and hypothesis-driven models and that was accepted by Health Authorities. We developed a tissue RO model in order to fill the gap between the available biomarkers and our understanding of the mode of action of ianalumab. The selected dose range aimed at providing a wide spread of drug exposures in order to mitigate the risk associated with the assumptions behind the tissue RO model. Such a range will enable characterization of the exposure-response relationship with clinical endpoints and thus inform the Phase 3 dose(s) to be tested in pSS patients.

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III-15: *Guillaume Baneyx* Target-mediated drug disposition modeling of lacnotuzumab in healthy volunteers and patients with advanced malignancies and triple negative breast cancer.

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Objectives: Lacnotuzumab is an IgG1/κ humanized monoclonal antibody directed against human macrophage colony stimulating factor (CSF-1) known as the primary regulator of survival, differentiation and function of M2 macrophages promoting tumor [1]. Pharmacokinetics of lacnotuzumab was characterized by a target-mediated drug disposition (TMDD) in healthy volunteers. Lacnotuzumab is currently being explored in patients with advanced malignancies and triple negative breast cancer (TNBC). An over-expression of circulating total (free + complex) CSF-1 at baseline was observed in cancer patients and this might impact the dose-exposure relationship. The objectives were i) to develop a TMDD model to characterize the dose-target engagement relationship; ii) to use model-based simulation to determine the lacnotuzumab dose leading to a substantial depletion of circulating free CSF-1 in cancer patients.

Methods: In a first step, circulating free lacnotuzumab and total CSF-1 data collected in healthy volunteers after single IV infusion of lacnotuzumab (1-20 mg/kg) was used to select the TMDD model structure. In a second step, the data collected in cancer patients after IV infusion every 3 weeks of lacnotuzumab (1-10 mg/kg) combined with spartalizumab (advanced malignancies) or carboplatin/gemcitabine (TNBC) was incorporated into the analysis dataset to refine the model structure by considering the impact of circulating total CSF-1 over-expression at baseline in cancer patients. Circulating free lacnotuzumab and total CSF-1 samples were collected on days 1, 2, 4, 8 and 15 of cycles 1 and 4 as well as on day 1 of other cycles. Then, model-based simulations were performed for pre-defined dosing regimens (1-20 mg/kg Q3W). Simulated circulating free lacnotuzumab exposure metrics and free CSF-1 depletion at end of cycle 2 were compared by dosing regimens in healthy volunteers and cancer patients. Model parameters were estimated by a nonlinear mixed effect modeling approach using Monolix2016R1 [2].

Results: Circulating free lacnotuzumab and total CSF-1 kinetics were described by a full TMDD model [3] with typical values for linear clearance (CL) of 0.20 L/h, central volume of distribution (V1) of 3.64 L, peripheral volume of distribution (V2) of 2.65 L and inter-compartmental clearance (Q) of 0.71 L/h. CL and V1 parameters were found to increase with body weight. The circulating free CSF-1 kinetics was described with an indirect response model driven by a synthesis rate (kin) and degradation rate (kout). The estimated circulating free CSF-1 degradation half-life of 26 minutes was in agreement with usual short half-life of cytokines. The complex kinetics was described with a quick association rate (kon), a slow dissociation rate (koff) and an estimated apparent degradation half-life of 44 days. The measured circulating total CSF-1 at baseline was found on average a 3-fold higher level in cancer patients (associated to large variability) compared to healthy volunteers with corresponding median values of 6200 and 2200 pg/mL. Over-expression of circulating total CSF-1 at baseline in cancer patients was modeled by a combination of higher synthesis rate (kin) and lower degradation rate (kout). At doses ≤ 5mg/kg, the model-based simulations suggested a lower circulating free lacnotuzumab through concentrations at end of cycle 2 in cancer patients than in healthy volunteers probably due to higher CSF-1 expression in cancer patients. At higher doses, the difference was limited probably due to target saturation in both populations. Based on current limitations

and assumptions, model-based simulations suggested on average a circulating free CSF-1 depletion (% of baseline) of 85 and 98 % in cancer patients for 5 and 10 mg/kg Q3W dosing regimens, respectively.

Conclusions: A full TMDD model was developed to describe the dose-target engagement relationship in both healthy volunteers and patients with advanced malignancies and triple negative breast cancer. Based on current limitations and assumptions, model-based simulations suggested that on average a substantial depletion of the circulating free CSF-1 would be achievable for the administrated dosing regimens in cancer patients. In future developments, the current model will be refined by considering the positive correlation between circulating total CSF-1 at baseline and baseline tumor size. Several TMDD approximations will be tested.

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III-16: *Catalina Barceló* Modelling waist-hip ratio increase in HIV-infected individuals starting antiretroviral therapy

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Objectives: The waist-hip ratio (WHR, unitless) is an anthropometric indicator of body fat distribution, calculated by dividing the circumference of the waist by the hip. A WHR above 0.9 in men and above 0.85 in women suggests abdominal obesity, which is associated with an increase in cardiovascular (CV) risk[1]. Increased abdominal fat is common among HIV-infected individuals and an increase in body weight and body mass index (BMI) frequently occurs during the first years of antiretroviral therapy (ART)[2, 3]. The assessment of abdominal obesity over time and its relationship with other risk factors might help the early detection of HIV-infected individuals at higher CV risk. The aims of this study were to develop a population model characterizing WHR trajectory after ART initiation and to quantify the demographic, clinical and pharmacological factors associated with the increase in abdominal obesity.

Methods: We included Swiss HIV Cohort Study (SHCS) participants who initiated ART after 2005 and had at least one WHR measurement close to ART initiation date and at least one other measurement after 2011 (n=1000). Longitudinal WHR data, covering a median follow-up of 8 years (range 4 to 12), were log-transformed to develop a piecewise-linear mixed-effects model (NONMEM 7.4). Structural models with one, two and three slopes corresponding to different time intervals of WHR changes were evaluated. The individual characteristics tested in the stepwise covariate model (scm, forward p=0.05 and backward p=0.005) building tool (PsN v.4.2) were age, gender, ethnicity, CD4 nadir, BMI, smoking, intravenous drug use, diabetes mellitus, and hepatitis C virus infection. The impact of ART was studied in a subpopulation of patients that maintained the same ART regimen over the period determined by the first and second slopes of the model.

Results: A piecewise-linear model with three slopes, dividing the WHR time course from ART initiation to 2.5 years ($SL_{0\text{-}2.5y}$), from 2.5 to 4 years ($SL_{2.5\text{-}4y}$) and from 4 years until last follow-up ($SL_{>4y}$), best described the data (ΔOFV= -716 and ΔOFV= -236, compared to one and two-slope models respectively). The final model estimated an average baseline WHR (WHR_0) of 0.90 in men and 0.84 in women with 4.9% of between-subject variability (%CV), a first slope $SL_{0\text{-}2.5y}$ of 0.039 WHR units/10 years (254%), a second slope $SL_{2.5\text{-}4y}$ of 0.043 WHR units/10 years (470%), and a third slope $SL_{>4y}$ of 0.028 WHR units/10 years (348%). An exponential error model adequately described the residual variability. Age and BMI at baseline were associated with an increase in WHR_0 by 14% in obese (BMI=40 kg/m^2) compared to individuals in the normal weight range (BMI=20 kg/m^2) and by 5% in 60 years old (95th percentile, P_{95}) compared to 40 years old (P_{50}) individuals. CD4 nadir <100 cells/µL increased $SL_{0\text{-}2.5y}$ by 150% and $SL_{>4y}$ was 135% higher in Africans and Hispanic Americans compared to other ethnicities. The univariate covariate analysis, in the subpopulation with the same ART regimen during the first 2.5 years (n=707), showed a reduction by 67% on $SL_{0\text{-}2.5y}$ in individuals on protease inhibitor-based regimens that was not retained in the multivariate analysis. In addition, maraviroc-based regimens increased $SL_{0\text{-}2.5y}$ by 5 fold without reaching statistical significance, due to the limited number of individuals in this group (n=4). No ART drug classes showed a significant influence on $SL_{0\text{-}2.5y}$ or $SL_{2.5\text{-}4y,}$ when analysed in the subpopulation that kept the same regimen over the first 4 years of treatment (n=555).

Conclusions: This model revealed an average WHR_0 close to the established cut-offs for risk prediction and an average gain of 0.03 WHR units over the 10 years after ART initiation, in line with previous studies(2, 3). Factors such as gender, age, BMI, CD4 nadir and ethnicity showed a considerable effect on abdominal obesity prevalence and change over time. We previously reported on similar findings regarding BMI increase in SHCS participants initiating ART(4, 5). Although the covariate analysis exposed several risk factors associations, an important part of the between-subject variability remained unexplained, which underlines the intricate and multifactorial nature of this obesity trait. Such a model, further refined according to genetic markers, might inform CV risk factor management in the HIV-infected population.

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III-17: *Christian Bartels* ggPMX: a toolbox to easily generate a comprehensive set of model diagnostic plots for population models

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Objectives:

A comprehensive and concise set of informative model diagnostic plots is primordial for the development of population PK and PKPD models. Even though the generation of any individual model diagnostic plot is fairly straightforward, generating a comprehensive set of plots adapted to a particular project takes time, tends to be reprogrammed for each new modeling activity, and tends to be done somewhat differently by different pharmacometricians. At Novartis, we aimed at standardizing the set of diagnostic plots used for modeling activities in order to reduce the overall effort required for generating such plots. For this, we developed a guidance that proposes an adequate set of diagnostics and a toolbox, called ggPMX and presented hereafter, that allows generating such diagnostics at a quality sufficient for publication and submissions.

Methods:

ggPMX is an R package, i.e., a set of functions written in the R language, which is familiar to many pharmacometricians. The key components of the package are the Reader, the Generator, the Controller and the Reporter. The Reader reads model outputs from different sources (i.e. text files containing population parameters, model predictions, individual random effects, simulations and data-related inputs like covariates) and restructures these outputs into standard formats, which can easily be processed by the Generator. The Generator contains R language code to produce the plots and is factorized into a small set of flexible key functions. A set of default plots is defined in a configuration file. The configuration file can be adapted, e.g., to have different configurations for different types of modeling activities. The user will call Generator functions via wrapper functions in the Controller to produce either all the default plots or selected plots of interest. In addition to editing the configuration, the user has different options to adapt aspects of the plots to specific requirements. Plots may be adapted by setting parameters of the wrapper function that generate the plots; there exist additional wrapper functions to change aspects of the existing default plots; and the plots are, in general, returned as ggplot objects that can be further customized using ggplot functionality. The Controller serves as a user interface in order to maintain user input data as well as to call other modules. The Reporter generates sets of graphs and tables and integrates them into an output file with annotations.

Results:

Using a simple, user-adaptable wrapper function, the toolbox can produce different model diagnostic plots (e.g. residual and EBE-based plots assessing possible trends and the shape of the distributions such as IWRES vs IPRED, VPCs, observations vs predictions, etc.). By default, the output file generated by the Reporter contains the diagnostics proposed in the Novartis internal guidance; however, these can be adapted to produce different sets of diagnostics as desired by the user, and any of the plots may be customized individually. The types of customizations include modifications of the graphical parameters and stratifications. ggPMX supports the generation of an output file (PDF or Word) containing diagnostic plots

for any model with a few lines of code by the user. The package is planned to be made available to the user community on CRAN at large.

Conclusion:

The first release of ggPMX will work with Monolix outputs and produce the necessary diagnostic plots mentioned in the Novartis internal guidance. Current plans are to enhance ggPMX to support NONMEM and nlmixr outputs as well.

III-18: *Roberta Bartolucci* A PBPK model for the study of Azathioprine pharmacokinetics in rats and prediction in humans

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Objectives: The aim of this work was to develop a mechanistic model for the description of the pharmacokinetics of the drug Azathioprine in rats, in order to predict the plasma concentration-time curve in humans. Azathioprine (AZA) is an immunosuppressive, antimetabolite prodrug used for the treatment of Acute Lymphoblastic Leukaemia in childhood and autoimmune disorders [1]. After absorption, it is rapidly converted into 6-mercaptopurine (6MP) which in turn is subject to a fast and extensive metabolism, distributed in several different tissues [1]. Despite AZA is a drug already on the market, it is still very studied for the Drug-Drug Interaction (DDI), as many drugs act on the same enzymes involved in its metabolism. A good description of AZA pharmacokinetics is therefore essential to better understand the DDI mechanism and to avoid toxic effects.

Methods: Physiologically-based pharmacokinetic (PBPK) models were chosen to describe the plasma concentration vs time profiles of AZA and 6MP in rats and humans, as they allow to consider inter-species differences in terms of physiological and anatomical characteristics [2]. Two coupled PBPK models have been developed in MATLAB, each one describing the kinetics of one molecule within the whole organism. The model structure was divided into 17 homogeneous (well-stirred) compartments: Lungs, Heart, Brain, Adipose tissue, Muscles, Spleen, Liver, Stomach, Intestinal lumen, Enterocytes, Gut tissue, Kidneys, Arterial Plasma, Venous Plasma, Arterial Red Blood Cells (RBC), Venous RBC and Rest of Body (representing all tissues not directly modelled). An ACAT model of 8 compartments was then implemented to better describe the absorption and the metabolism in the intestinal mucosa. Partition coefficients of each compartment, except RBC's, were estimated using Poulin-Thiel equations with a correction factor K that considers active transports. Drug exchange between plasma and RBC compartments has been modelled through the PSBC parameter, which takes into account the permeability and the membrane surface area. The conversion of AZA into 6MP was represented with a first order clearance in Liver and Enterocytes, whereas the metabolism of 6MP was described by Michaelis-Menten equations in Liver, Enterocytes, RBCs and Kidney.

Results: Three scenarios (Intravenous administration of 6MP, oral administration of 6MP and oral administration of AZA) were simulated in rats using pre-clinical experimental data [3]-[4], in order to estimate 7 PK parameters that have not been found in literature. After a proper parameter scaling between rat and human, the complete model thus obtained was used to simulate an oral administration of AZA in humans, and the predicted plasma concentration-time profile of 6MP was compared with literature data [5]. The estimated values of the unknown parameters allowed to obtain a simulated PK profile similar to the experimental data in rats and a good prediction in humans, with a plasma concentration curve of 6MP within the range of a standard deviation from the mean values. Cmax, Tmax and AUC were also comparable to literature values in every scenario.

Conclusions: The transition from the pre-clinical to the clinical phase, critical in drug development, it is generally addressed using empirical methods such as allometric scaling, which considers only the proportion with respect to the body weight [2]. In this work instead, a PBPK model was used to considers the anatomical and physiological differences between rats and humans. Furthermore, the mechanistic

description of AZA and 6MP metabolism in rats allowed to obtain a good prediction of the plasma concentration in humans. For this reason, the model will could be useful for further DDI investigations.

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III-19: *Carla Bastida Fernández* PK/PD of the individual components of composite indexes variables used for disease activity assessment in rheumatoid arthritis patients on tocilizumab treatment.

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Introduction: Tocilizumab (TCZ) is a humanized anti-IL-6 receptor monoclonal antibody that has shown efficacy in the management of moderate to severe rheumatoid arthritis (RA) [1]. Disease activity in RA patients is routinely assessed using composite indexes that include clinical and/or laboratory variables. We find the disease activity score using 28 joint counts (DAS28) in its two versions employing erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and the simplified and clinical disease activity scores (SDAI and CDAI, respectively). Formulas are shown below:

- DAS28-ESR = 0.56*SQRT(TJC) + 0.28*SQRT(SJC) + 0.70*ln(ESR) + 0.014*PGA (mm)

- SDAI = SJC + TJC + PGA (cm) + EGA (cm) + CRP (mg/dL)

- CDAI = SJC + TJC + PGA (cm) + EGA (cm)

*EGA: global health assessment by the evaluator; PGA: global health assessment by the patient; SJC: swollen joint count; TJC: tender joint count.

These composite indexes assume all variables to have the same dynamics but on TCZ treatment, it has been reported that inflammatory markers (CRP and ESR) show faster response compared to clinical variables, which complicates interpretation of these composite indexes [2].

Objectives: The purpose of the study was to assess the dynamics of the different individual variables included in composite indexes in RA patients on treatment with intravenous (iv) TCZ using a modeling approach.

Methods: Pharmacokinetic and clinical data were obtained from a prospective, observational, single-center study involving 35 subjects with RA treated with iv TCZ at a dose range from 4 to 8 mg/kg every 28 days. Clinical data and levels of inflammation markers such as CRP and ESR were retrospectively collected from the beginning of TCZ treatment every 28 days until the moment of inclusion at the PK study. A PK/pharmacodynamics (PKPD) model was developed using a previously published PK model and non-linear mixed-effects modeling implemented in NONMEM v7.3 [3].

Results: The relationship between TCZ concentration and disease activity was described using an indirect response model with inhibition of the variable input (K_{in}). Dynamics of the PD data could be adequately described grouping them in slow-decreasing variables (for tender and swollen joint counts and patient and evaluator global health assessment) and fast-decreasing variables (for CRP and ESR). Slow decreasing variables show a higher EC_{50} (EC_{50}: 6.98 µg/mL (RSE 6.7%, IIV: 155%)) and a lower maximum effect (E_{max}: 0.765 (RSE 2.8%)) and output constant (K_{out}: 0.00117 h^{-1} (RSE 12%, IIV: 73.6%)) than the fast decreasing

variables, which have an EC_{50} of 1.06 µg/mL (RSE 22.5%, IIV: 103%), E_{max}: 1 (not estimated) and K_{out}: 0.00245 h^{-1} (RSE 15.6%, IIV: 68.8%).

*EC_{50}: concentration at which 50% of the maximum effect is reached; IIV: inter-individual variability; RSE: relative standard error.

Conclusions: Higher serum TCZ concentrations are needed to normalize tender/swollen joint counts and health assessment values than to normalize inflammation markers such as CRP and ESR. Moreover, composite indexes that include fast-decreasing variables in their formula (DAS28-ESR and SDAI), would overestimate the number of patients in remission at the beginning of the treatment with TCZ.

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III-20: *Ryan Beechinor* A population pharmacokinetic study of high dose methotrexate treatment in infants with acute lymphoblastic leukemia: The importance of modeling inter-occasion variability across treatment cycles

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Introduction: Infants with acute lymphoblastic leukemia (ALL) treated with high dose methotrexate (MTX) may have reduced MTX clearance (CL) due to renal immaturity present at birth, which may predispose them to toxicity [1-2].

Objectives:

- Develop a population pharmacokinetic (PK) model of MTX in infants with ALL
- Characterize the impact of interoccasion variability (IOV) on this model
- Apply the model with simulations to evaluate the impact of various doses on MTX exposure

Methods: MTX concentrations were obtained from infants enrolled in the Children's Oncology Group (COG) Clinical Trial P9407. A MTX PK database was developed by combining MTX PK data from 18 infants enrolled in a PK substudy with MTX PK data collected from 56 infants as part of routine care. All subjects were screened for adequate organ function prior to MTX treatment, including a creatinine CL >70 mL/min/1.73 m^2. Each infant received MTX 4 g/m^2 intravenously (IV) for four cycles during weeks 4, 5, 11, and 12 of intensification chemotherapy. A total of 711 MTX plasma concentrations were available from 74 infants treated with 234 cycles of high dose MTX. Median (range) baseline demographics of infants enrolled in this study included a post-natal age (PNA) of 7.5 months (2-12), total body weight of 8.8 kg (4.5-11.9), height of 69 cm (51-78), and body surface area of 0.40 m^2 (0.24 – 0.48). A population PK analysis was performed using NONMEM® version 7.4 [3]. The impact of patient demographics was explored in a covariate analysis, and interindividual (IIV), IOV, and residual variability were estimated. Covariates tested on CL and volume of distribution (Vd) parameters included total body weight, post-natal age, height, and body surface area. The final model was evaluated using a nonparametric bootstrap analysis and a visual predictive check using Perl-speaks-NONMEM (version 3.6.2) [4-5]. Simulations were performed to assess the frequency of subtherapeutic and supratherapeutic MTX concentrations with doses ranging from 2 – 8 g/m^2 of MTX given IV over 24 hours. For these simulations, a virtual population of 1000 infants was created, and MTX concentrations at 24, 48, and 72 hours were simulated. Target MTX concentrations were defined based on previous literature suggesting that MTX concentrations <16 µM at 24 hours are associated with relapse and subthe rapeutic, and MTX concentrations >1.0 µM at 48 hours or >0.1 µM at 72 hours are associated with renal toxicity and supratherapeutic [6-7].

Results: MTX plasma concentrations were best described by a two compartment model with linear elimination. After allometrically scaled total body weight was incorporated into CL and Vd terms, no other covariates were found to be significant. The final model included IIV on CL and central Vd, and IOV was included on CL. The mean (% relative standard error) final model parameter estimates allometrically scaled to a 70 kg adult were as follows: a CL of 10.9 L/h (3.0%), a central Vd of 62.6 L (4.9%), a peripheral Vd of 12.7 L (8.2%), and an intercompartmental CL of 0.128 L/hr (7.2%). The coefficient of variation for IOV was

relatively high at 26.1%, compared to the IIV for CL and central Vd, 10.6% and 11.9% respectively. Simulations revealed that only the 2 g/m^2 dosing regimen resulted in simulated 24 hour MTX concentrations <16 µM, and this occurred at a low frequency (2.4%). Additionally, compared to the study does of 4 g/m^2 , escalating doses of 6 g/m^2 and 8 g/m^2 resulted in a greater percentage of simulated MTX concentrations in the supratherapeutic range at 72 hours, with 29%, 44%, and 57% of infants, respectively.

Conclusions: This is first population PK model of high dose MTX in infant ALL to include subjects as young as 2 months PNA. Infants in this study demonstrated a similar magnitude of IOV in their CL of MTX compared to previous studies performed in children [8]. Variation in the CL of MTX across cycles may be explained by changes in disease progression, drug-drug interactions, or unmeasured covariates which vary across cycles. The magnitude of IOV in the CL of MTX suggests that Bayesian adaptive dosing algorithms may be optimized by obtaining MTX concentrations during the current cycle infusion rather than concentrations measured from previous cycles. Our simulations revealed that dosing regimens of 2-8 g/m^2 are likely to provide sufficient MTX exposure, however, increasing doses of high dose MTX above 4 g/m^2 may result in untoward renal toxicity.

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III-21: *Amina Bensalem* Concentration-effect relationships of therapeutic monoclonal antibody rituximab in rheumatoid arthritis.

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Objectives: Rituximab (RTX) is approved as a second line treatment in active rheumatoid arthritis (RA) in combination with methotrexate, but there is a large inter-individual variability in clinical response. A better response was previously associated with a decrease in CD4+ T cell counts [1, 2]. However, no PK–PD study of RTX in RA is available. This study aimed at quantifying the contribution of CD4+ T cell decrease in the clinical response in RA patients treated with RTX.

Methods: In this retrospective monocentric observational study, 52 patients were assessed. All patients had received 2 infusions of 1000 mg of RTX 2 weeks apart. Peripheral blood CD4+ counts and disease activity score in 28 joints (DAS28) were used as biomarker of effect and modeled as a dependent variable. RTX serum concentrations, peripheral blood CD4+ counts, and DAS28 were measured before and after each RTX infusion and at 3, 6 and 9 months after last infusion. A population PK-PD model was developed using Monolix Suite 2016R1, where a between-subject model mixtures (BSMM) was implemented to well describe the clinical response in patients with and without CD4+ cell decrease and estimate the probability of CD4+ counts decrease. A turnover model was used to describe the effect of RTX on CD4+ T-cell counts, whereas a direct model was used to describe both RTX and CD4 + T cell count effect on DAS28.

Results: Our PK–PD model described the data satisfactorily. The probability of CD4+ counts decrease was estimated at 0.75. Patients with a CD4+ decrease had a higher ΔDAS28 than the patients without CD4+ decrease, with a maximal ΔDAS28 of -1.34 and -0.64 in patients with and without CD4+ cell decrease, respectively. Moreover, at M6, patients with CD4+ cell decrease had a median DAS28 of 3.5 (IQR: 2.7 - 4.4), among them 39.5 % with low disease activity (DAS28≤ 3.2) and 22.3 % in remission (DAS28< 2.6). At the same time point, median DAS28 of patients without CD4+ cell decrease was 4.3 (IQR: 3.5 – 5.1), among them 17.7 % with low disease activity, and 8.6 % in remission.

Conclusions: This is the first study describing concentration-effect relationship of RTX in RA patients, using well-defined biological and clinical outcomes, as measured by CD4+ counts and DAS28 respectively. Our results confirmed that clinical improvement of RA patients after RTX treatment is partly dependent on the mechanism of CD4+ cells, and quantified the proportion of both RTX concentration and CD4 counts that induces DAS28 decrease.

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III-22: *Agathe Béranger* Piperacillin dosing regimen optimization in critically ill children according to different creatinine clearances

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Objectives: Pharmacokinetic parameters are altered in critically ill patients, leading to a reduction of the beta-lactam concentrations. For instance, in adult patients, it has been well demonstrated that augmented renal clearance results in subtherapeutic antibiotic concentrations. Moreover, there is a large between subject variability in children. Our objectives were to build a pediatric population pharmacokinetic model for Piperacillin, in order to optimize individual dosing regimen.

Methods: All children admitted in pediatric intensive care unit, aged less than 18 years, weighing more than 2.5 kg, and receiving intermittent Piperacillin infusions were included. Blood samples (1 mL on heparin tube) were collected during routine laboratory tests, part of patient clinical routine care. Piperacillin was quantified by high performance liquid chromatography. To create a population pharmacokinetics model, Piperacillin data was analyzed using non-linear mixed effect modelling software (MONOLIX, version 2016R1), along with the SAEM algorithm. Models were coded with differential equations in a MLXTRAN script file. Monte Carlo simulations were used to optimize dosing regimen, in order to maintain Piperacillin plasma concentration above the minimum inhibitory concentration (16 $mg.L^{-1}$ for *Pseudomonas aeruginosa*) throughout the dosing interval (100% $fT_{>MIC}$).

Results: We included 50 children with a median (range) post natal age of 2.3 (0.1-18) years, body weight of 11.9 (2.7-50) kg, PELOD-2 severity score of 4 (0-16), and estimated creatinine clearance (eCCL) of 142 (29-675) $mL.min^{-1}.1.73m^{-2}$. A one-compartment model with first-order elimination adequately described the data. Median (range) values for piperacillin clearance and volume of distribution were respectively 3 (0.71-10) $L.h^{-1}$ and 0.33 (0.21-0.86) $L.kg^{-1}$. Body weight was integrated with the allometric relationship. eCCL and PELOD-2 severity score were the covariates explaining between subject variability on clearance and volume, respectively. A third of the cohort attained the target, according to our dosing regimen and to the European and American guidelines. Monte Carlo simulations were conducted with two daily dosing regimens: 300 $mg.kg^{-1}.day^{-1}$ for normal clearance (40-130 $mL.min^{-1}.1.73m^{-2}$), and 400 $mg.kg^{-1}.day^{-1}$ for eCCL > 130 $mL.min^{-1}.1.73m^{-2}$. According to the simulations, for children with normal and augmented renal clearance, continuous infusion provided the highest probability to reach the target, with dosing regimen of 300 and 400 $mg.kg^{-1}.day^{-1}$ respectively.

Conclusions: To reach the target of 100% $fT_{>MIC}$, standard intermittent Piperacillin dosing regimen in critically ill children is not appropriate. In addition to body weight, dosing regimens should take into account the creatinine clearance and the PELOD-2 severity score. Continuous infusion is the most adequate dosing regimen for children with augmented renal clearance. Piperacillin individualized dosing regimens and therapeutic drug monitoring are mandatory in pediatric intensive care unit.

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III-23: *Agnieszka Bienert* Pharmacokinetics of dexmedetomidine in elderly patients undergoing sedation after abdominal aortic surgery.

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Objectives: Dexmedetomidine (DEX) is an α2-agonist which has been increasingly used for analgosedation. The aim of this study was to characterize the population pharmacokinetics (PK) of dexmedetomidine in patients undergoing sedation after abdominal aortic surgery and to investigate the potential benefits of individualization of drug dosing based on patients' characteristics including genetic polymorphism. DEX is a highly extracted drug with the hepatic extraction ratio of 0,7 [1], therefore cardiac index and other cardiovascular parameters were also taken into account as potential covariates.

Methods: Dexmedetomidine (Dexdor, Orion Pharma Poland Sp. z.o.o.) was administered by continuous intravenous infusion without a loading dose. The infusion was started at the rate of 0.7 µg/kg/h and titrated to achieve the desired level of sedation according to the monitored bispectral index (BIS, Philips Medical Systems B.V, Netherlands). BIS values were kept between 60 and 80. Cardiac index (CI), a hemodynamic parameter related to cardiac output was measured and recorded by FloTrac System (Edwards Lifescences, USA). Blood samples for DEX assay were collected daily during the infusion and at the selected time points after its termination. The DEX concentrations in the plasma were measured using LC-MS/MS method. The following covariates were examined to influence DEX PK: patients' age, sex, body weight, systolic and diastolic blood pressure, heart rate, cardiac index, infusion duration as well as CYP2C19, CYP1A2, CYP2A6, UGT1A4 and UGT2B genetic polymorphism. Non-linear mixed-effects modelling in NONMEM (Version 7.3.0, Icon Development Solutions, Ellicott City, MD, USA) was used to analyze the observed data.

Results: Concentration-time profiles of DEX were obtained from 11 male and 1 female elderly patients, with the median age of 64.5 (range between 61 and 79 years). Duration of infusion was less than 24 hours in all patients. The DEX PK was best described by a two-compartment model. The typical values of PK parameters were estimated as 53.4 L for the volume of the central compartment, 112 L for the volume of the peripheral compartment, 51.1 L/h (for a 70 kg patient) for systemic clearance and 36.7 L/h for the distribution clearance. Those values are consistent with literature findings. We were unable to show any significant relationship between collected covariates and DEX PK.

Conclusions: This study does not provide sufficient evidence to support the individualization of DEX dosing based on age, sex, body weight, cardiac index, examined CYP and UGT enzymes polymorphism and infusion duration.

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III-24: *Robert Bies* Pharmacokinetic-pharmacodynamic modelling of MK-2048 in ex vivo cervical tissue

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Objectives:

An estimated 1.8 million individuals worldwide acquired new HIV infections in 2016; the equivalent of around 5,000 new infections per day. The development of safe and efficacious HIV prevention strategies is therefore a global health priority. The Film Antiretroviral Microbicide Evaluation (FAME) program aims to incorporate MK-2048 – a potent HIV integrase inhibitor developed by Merck & Co., Inc., Kenilworth, NJ, USA - into a vaginal film formulation capable of providing one week of coitally independent protection from HIV infection from unprotected vaginal intercourse. This work focuses on characterizing the extended pharmacokinetic (PK) and pharmacodynamic (PD) properties of MK-2048 in HIV-1 infected human cervical tissue explants.

Methods:

The extended PK data explant study included three cervical tissue samples (subjects) treated with 100 µM of MK-2048; two tissues per explant per time point. The samples were washed and frozen at 0, 0.5, 1, 6, 24, 48, 72, 96 & 120 hours. Homogenate tissue concentrations were fitted to a PK model using non-linear mixed-effects modelling implemented in NONMEM V7.3.0 [1]; initial amounts of MK-2048 were set to concentrations observed in 0-hour samples. The PK-PD explant study included five tissues (subjects) with 2-explants per tissue, per treatment group. Explants were infected overnight with HIV-1 in the presence or absence of MK-2048, then washed and serially sampled for HIV-1 p24 antigen at 1, 4, 7-8, 11, 14-15, 17-18 & 21-22 days. For each tissue and treatment group, two additional explants were used for MK-2048 PK measurements on day 1. The viral dynamics of the control group were fitted to a PD model using non-linear mixed-effects modelling implemented in NONMEM V7.3.0; tissue PK parameters were fixed to those fitted in the extended PK model. Different PD growth models were tested including linear, exponential, simeoni (linear followed by exponential growth and transit compartments for damage phase) [2], signal distribution (with a differing number of transit compartments) [3] and the Perelson model of HIV dynamics [4].

Results:

The PK of MK-2048 was well characterized by a 2-compartment model with linear elimination. The coefficient of variation (CV) for the residual variability was 19% within replicates and 15% CV was found for other sources. The between-subject variability on drug elimination rate was 1008% CV with a 67% relative standard error. Viral growth for the control group (i.e. samples treated with HIV only) was best characterized using the Perelson model including uninfected target cells, infected cells and free virus.

Conclusions:

The extended PK model predicted MK-2048 drug concentrations in cervical tissue and the Perelson model best described viral dynamics in the control group of the human explant tissue. The final extended PK and

control PD models informed the PK-PD modelling process of this new compound and the HIV-1 viral dynamics in human explant studies. The results of this work can provide suggestions on the concentration of MK-2048 required to prevent viral replication in humans. They can be incorporated in to physiologically-based pharmacokinetic (PBPK) models of vaginally administered drugs to predict patient concentration time profiles *in vivo* and used to develop PBPK-PD models able to predict whether MK-2048 is likely to prevent new, sexually-transmitted, HIV-1 infections.

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III-25: *Henrik Bjugård Nyberg* A pediatric population pharmacokinetic model for ethionamide in South African children treated for drug-susceptible or drug-resistant tuberculosis.

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Objectives: As drug resistant tuberculosis becomes more prevalent, improved knowledge of drugs also beyond first-line treatment becomes increasingly important. Ethionamide is used both in first-line and second-line treatment of tuberculosis, including in tuberculous meningitis [1] but the current understanding of its pharmacokinetics (PK) is limited, especially in children. Ethionamide metabolism follows a range of different pathways, with the most prominent being the flavin-dependent monooxygenases found in both humans and in Mycobacterium tuberculosis. This pathway is also the activation mechanism for this pro-drug [2]. The aim of the study was to develop a pediatric population PK model for ethionamide.

Methods: Pharmacokinetic data on ethionamide in children was pooled from 2 observational clinical studies [3,4] conducted in Cape Town, South Africa. The first study contributed 110 children on treatment for multi-drug resistant tuberculosis (MDR-TB), while the second contributed 9 young children (3 mos – 2.5 yrs) treated for drug-susceptible TB. The two studies otherwise had very similar study procedures and demographics. Overall median age was 2.6 years (range: 3 mos – 15 yrs), and their weight median was 12.5 kg (range: 2.5–66 kg). Children received ethionamide once-daily with weight-based dosing of 20 mg/kg up to a maximum of 1,000 mg, in combination with other first- or second-line antituberculosis medications, and with antiretroviral therapy (ART) in the case of HIV co-infection.
Twenty-four of 119 children were HIV-positive, mainly on lopinavir/ritonavir-based ART therapy; 21 were simultaneously treated with rifampicin. Smaller children received crushed tablets (n=101), due to lack of child-friendly formulations, often using a nasogastric tube (n=82) on the day of sampling. Blood samples were collected pre-dose and at 1, 2, 4, 6 (study 2), 8, and 11 (study 1) hours post-dose. The samples from both studies were analyzed in the same laboratory using LC-MS/MS with a validated method; the limit of quantification (LLoQ) was 0.0313 mg/L.

Model development was performed in NONMEM 7.4 [5] using improvements in likelihood, diagnostic plots, and physiological plausibility as criteria for selection. The effects of body weight and fat-free mass (FFM) were investigated using allometric scaling, and that of age, using a maturation function. Other potential covariates such as HIV-status, weight-for-age Z-scores, administration method (crushed vs whole tablet, swallowed vs nasogastric tube) and concomitant medications were explored using step-wise covariate modelling in the PsN software [6]. Several models for absorption and disposition were compared. A combined proportional and additive error model was used, and data below LLoQ was handled using the M6 method [7].

Results: Ethionamide PK in children was best described by a one-compartment disposition model with transit compartment absorption [8] and first-order elimination. Volume of distribution (V) and clearance (CL) were scaled by weight and FFM, respectively. For a typical child weighing 12.5 kg (10 kg of FFM), the model estimated the typical value of CL to be 9.3 L/h and of V to be 21.2 L. A maturation function for

clearance improved model fit, but ultimately needed to be stabilized by a weakly-informative prior. Clearance was expected to reach 50% of its mature value one month after birth. HIV-co-infected children had 21% lower bioavailability. A faster absorption (40% shorter mean transit time, MTT) was found in children receiving crushed tablets with or without nasogastric tube, but no difference was found in bioavailability. No drug-drug interactions were identified, most notably with rifampicin, an inducer of several drug-metabolizing enzymes. The stochastic model supported inter-individual variability for clearance (28%) as well as inter-occasion variability for bioavailability (37%) and MTT (62%).

Conclusions: We propose a model that successfully describes ethionamide pharmacokinetics in children, and that could be used for optimization of dosing regimens. The model detects a faster than expected maturation function, which may be a feature of the complex metabolism of ethionamide. The observed HIV effect may be due to one of the concomitantly administered antiretroviral drugs, but with the limited current data we were unable to confirm the precise cause this effect. Crushing tablets or using a nasogastric tube affects the speed, but not the extent of absorption.

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III-26: *Alessandro Boianelli* A quantitative systems pharmacology model for understanding the role of dietary fructose metabolism in NAFLD

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Objectives: Increased fructose consumption has been suggested to contribute strongly to the de novo lipogenesis and consequently to the non-alcoholic fatty liver disease, dyslipidemia, and insulin resistance. However a causal role of fructose in these metabolic diseases remains debated [1]. Quantitative systems pharmacology models can represent an important and useful tool to improve the holistic understanding of the correlation between the fructose metabolism and lipid accumulation via *de novo* lipogenesis pathways. To this purpose, the main objectives of this work are:

- develop a mechanistic mathematical model to better understand the acute and long term effect of high fructose diet on non–alcoholic fatty liver disease biomarkers *in vivo*;
- elucidate the relative importance of enzymatic pathways involved in fatty acids and triglycerides formation
- prioritize specific therapeutic targets in the de novo lipogenesis pathways

Methods: the quantitative systems pharmacology model based on the ordinary differential equations consider as compartments the portal vein, the plasma and the hepatocytes cytosol: This last compartment encompasses the major pathways of fructose and glucose metabolism in the liver considering also the effects of hormonal (insulin and glucagon) and allosteric regulations. The reaction rates of the enzymatic processes follow Michaelis-Menten and Hill function form. The kinetic parameters and the initial conditions for the metabolites included in the model were fixed according to the concentration values present in literature [2], [3] and BRENDA database [4]. Experimental data were generated using C57BL/6 mice receiving a 2 g/kg dose of fructose administered either orally or intraperitoneally. Fructose and fructose 1-phosphate, as the first biomarker in the fructose pathway, concentrations were measured in plasma, portal vein and liver every 15 min for 3 hours. Moreover, in order to evaluate the long term effect of fructose intake on NAFLD biomarkers (liver triglycerides, free fatty acids, glucose, lactate and glycogen), we simulated a high fructose diet for 12 weeks with two different intake rate of 0.8 g/kg and 2 g/kg every 2 hours respectively. All the model simulations for the acute and long term fructose intake were performed using MATLAB R2016b.

Results: Fructose and fructose 1-phosphate concentration in the liver were described adequately by the mathematical model. The fructose was already absorbed in the portal vein and in the liver within 15 min after fructose challenge and returned at steady state level in 2 hours. Consequently the fructose 1-phosphate concentration showed the same temporal profile as fructose. Moreover during the same observation time, model simulations revealed modest production of glucose, glycogen and lactate. The same pattern was also conserved for liver triglycerides and fatty acids. On the contrary, the long term high fructose diet simulations showed an increase of liver glucose from 5.5 mM to 6.8 mM and lactate concentrations changing from 1 mM to 1.2 mM. Furthermore, liver triglycerides level after the high fructose diet exhibited a steady state level of 48 mM compared to the physiological level considered (32 mM). Interestingly, the two fructose intake levels presented the same steady state levels for the biomarkers considered.

Conclusions: We developed a quantitative systems pharmacology model for the fructose metabolism in the liver. The model was able to reproduce experimental data obtained in mice. The long term high fructose diet simulations showed a severe increase of liver triglycerides, thus suggesting the possible role of fructose to contribute to the development of metabolic syndrome.

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III-27: *Charlotte Bon* Capacity limits of ASGPR mediated liver targeting

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Objectives:

Efficient delivery of therapeutic molecules into the targeted tissues and cells remains a limiting factor for antibody based therapies and the wider use of new therapeutic technologies such as nucleic acid therapeutics and CRISPR mediated gene editing [1, 2]. The abundant cell surface asialoglycoprotein receptor (ASGPR) is a highly selective receptor found on hepatocytes with a high potential for being exploited as a selective shuttle for delivery. Various nucleic acid therapeutics that bind to this receptor are already in clinical development. Despite its high capacity, this receptor mediated delivery mechanism can be saturated resulting in a reduced selectivity for the liver and therefore increase the likelihood for systemic adverse effects. Therefore, it is important to optimize both molecular properties and the administration protocol. To investigate the *in-vivo* drug delivery capacity of the ASGPR we here aim to exploit the Target Mediated Drug Disposition (TMDD) of a newly developed anti-ASGPR antibody (ASGPR Ab) in mice.

Methods:

The developed anti-ASGPR antibody was generated and first characterized in-vitro. Pharmacokinetic and biodistribution studies were performed in mice and analyzed by modeling. The ASGPR antibody was administered via intravenous administration or subcutaneous dosing at doses ranging from 1 to 30 mg/kg. A mechanistically-based mathematical modeling approach was used for PK data analysis. The model was based on a generalized pharmacokinetic model for drugs exhibiting target-mediated drug disposition (TMDD) as originally described by Mager and Jusko in 2001 [3]. Parameters have been estimated using a non-linear mixed-effect approach in MONOLIX 4.3.3. A biodistribution study was performed using 111-indium radiolabeled ASGPR antibodies to assess the accuracy of the TMDD model in predicting the liver uptake. It is of note however that the liver has been found to be a major elimination organ for monoclonal antibodies. Therefore, a radiolabeled non-targeting antibody (IL17 Ab) was used for comparison. To be successful as a targeted therapy, the protocol of administration should be selected such as to maximize internalization into hepatocytes via the ASGPR route and minimize saturation that would lead to off-target distribution and unspecific clearance. Therefore, simulations were performed to show the influence of receptor saturation and frequency of administration on delivery efficiency (percentage of the dose distributed to the liver) and on the delivered quantity.

Results:

After IV and SC dosing, the PK profiles show non-linear concentration time profiles that are consistent with TMDD. Using pharmacokinetic data and an in-silico TMDD model we estimate an ASGPR expression level of 1.8 million molecules per hepatocyte in mice. The half-life of the degradation of the receptor was found to be equal to 15 hours and the formed ligand-receptor complex is internalized with a half-life of 5 days. The biodistribution study confirmed the specific uptake in liver in comparison with a non-targeting antibody. The kinetics of the ASGPR shows that a saturation of the shuttle at therapeutic concentrations is possible.

Indeed, it was shown that at 1mg/kg 96% of the total dose is predicted to be cleared via the target pathway while at 30 mg/kg this percentage drops to 76% due to receptor saturation. In addition, the rate at which free receptors become available again is critical to optimize a protocol of administration in the case of multiple dosing regimens. Therefore, simulations were performed to investigate how quickly the ASGPR system recovers from a dose challenge. The free receptors return to 90% of the baseline level in 3 days, while at 30 mg/kg it takes more than a week. Simulations were then performed to show the influence of receptor saturation, varying the administrated dose, and frequency of administration on delivery efficiency (percentage of the dose distributed to the liver) and on the delivered quantity. This optimization can also be extended to different modalities, to incorporate the different pharmacokinetic properties (non ASGPR related). For example, we examined what would be the impact of a faster clearance rate on the delivery efficiency.

Conclusions:

We proposed using the developed TMDD to support the development of therapies that use the ASGPR as a shuttle into hepatocytes.

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III-28: *Rolien Bosch* A novel integrated QSP model of in vivo human glucose regulation to support development of a glucagon/GLP-1 dual agonist.

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Objectives: MEDI0382 is a synthetic peptide with both glucagon-like peptide-1 (GLP-1) and glucagon receptor co-agonist activity. The combination of GLP-1 and glucagon activity has been shown to improve glycaemic control and lipid profiles, and cause significant weight loss in preclinical studies [1]. These effects are hypothesized to be mediated through stimulation of glucose-mediated insulin release (the incretin effect), delayed gastric emptying, and increased fatty acid oxidation. Mechanistic PKPD models are available to quantify drug effects on glucose, insulin and GLP-1 dynamics in humans [2-4]. However, the integrated interrelationship between glucagon and the GLP-1 and glucagon effects on gastric emptying has not been captured in these models. Hence, the aim of this research is to develop a quantitative systems pharmacology (QSP) model that characterises the interrelationship between glucose, insulin GLP-1, glucagon and glucose-dependent insulinotropic peptide (GIP), which can be used to support development of drugs modulating glucose regulation pathways.

Methods: A QSP model describing glucose, glucagon, GLP-1, GIP and insulin (4GI model) levels was developed using literature clinical data [2-10]. These data included various, non-pharmacological challenges to glucose regulated pathways (e.g. intravenous glucose, meals, glucagon and incretins). Mean data from three clinical studies (LEAD-3, LEAD-6 and AWARD-6), in which the effect of liraglutide (a GLP-1 agonist) on glucose and insulin was investigated, were added to the dataset to describe the effects of GLP-1 agonism [11-13]. The integrated glucose-insulin (IGI) model by Silber et al [2,3], in combination with knowledge from the Landersdorfer model [4], was used as a starting point, and glucose and insulin disposition parameters were fixed to the published values. The model was adjusted and extended to describe glucagon, GLP-1 and GIP dynamics. Liraglutide pharmacokinetics [14] was included to model the effects of liraglutide on glucose concentrations. The model was externally validated by predicting the effects of another GLP-1 agonist, dulaglutide, on glucose. For this, the 4GI model was combined with a published dulaglutide PK model [15], and used to predict the effects of dulaglutide on fasting and postprandial plasma glucose levels from the AWARD-6 study [13].

Results: The developed QSP model was shown to adequately describe glucose, insulin, GLP-1, GIP and glucagon dynamics. Important known feedback mechanisms could be identified with good precision (parameter CV < 50 %), and included glucose stimulation of insulin, glucose inhibition of glucagon, insulin stimulation of glucose clearance, GLP-1- and GIP stimulation of glucose-dependent insulin secretion, GLP-1 inhibition of glucose uptake, GLP-1 inhibition of glucagon, glucagon stimulation of glucose. Liraglutide effects on fasting and postprandial glucose levels were adequately described. External validation showed that the model can predict fasting and postprandial glucose levels after dulaglutide administration.

Conclusions: A novel integrated QSP model characterizing important known feedback mechanisms between glucose, insulin, glucagon, GLP and GIP (4GI) after food intake and/or drug administration was developed and externally validated using literature data. The 4GI model can be proposed as a quantitative decision making tool to support progression of novel molecules modulating these pathways. Future 4GI model features may include e.g. integrating mechanisms of energy expenditure and the effect of weight and lipid changes.

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III-29: *Ari Brekkan Viggosson* Characterization of anti-drug antibodies using a bivariate mixed hidden Markov model

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Objectives: Monoclonal antibodies are a well-established therapy for several chronic inflammatory diseases. A phenomenon observed with administration of this type of drugs, is the ability of the immune system to produce specific anti-drug antibodies (ADA), which may influence the pharmacokinetics (PK) of the drug and possibly affect efficacy and safety. Certolizumab Pegol (Cimzia®) is a PEGylated Fc-free anti-tumor necrosis factor α (anti-TNF-α) antibody used in the treatment of several inflammatory diseases including rheumatoid arthritis (RA). The ADA against Cimzia have been characterized with an ELISA technique in clinical settings and the incidence of immunogenicity in RA has been reported to be 9.6%, with transient and persistent PK effects[1]. There is an interest in characterizing the transient/persistent ADA and to investigate potential covariates and trial characteristics that may influence their occurrence. Due to drug interference with its measurement assay, false negative data may occasionally arise. Thus, in some patients, ADA may not be measureable despite the disposition of the drug being altered. In this work, a novel model-based method for ADA characterization is presented using mixed hidden Markov models (MHMM), allowing for inferences about ADA formation given a set of ADA and drug PK observations[2,3].

Methods: Phase II data from a clinical trial aiming to assess the efficacy and safety of 6 doses (50-800 mg) of Cimzia versus placebo administered Q4W in patients with RA was used in this work. The total number of evaluated patients was 239 with an average of ~9 observations over a maximum of 13 weeks. A previously developed PK model not including ADA as a covariate was fit to the first dosing occasion in the data with the subsequent dosing occasions being predicted from the resulting fit.The obtained PK individual weighted residuals (PK_{RES}) were used, in addition to ADA measurements (ADA_{MEAS}), as continuous observed variables to inform about the two states in a bivariate-MHMM (BV-MHMM). The hidden states in the model were no ADA (S_{NOADA}) and ADA production (S_{ADA}). The parameter estimates in the model were compared to expectations for the distributions of the observed variables and the model was used to calculate the most probable state sequence in each individual using the Viterbi algorithm. Estimation was done in NONMEM with IMPMAP.

Results: A BV-MHMM was established that included two states influencing PK_{RES} and ADA_{MEAS}, correlated through a bivariate normal distribution. Correlations between PK_{RES} and ADA_{MEAS} in S_{NOADA} (ρ_{NOADA}) and S_{ADA} (ρ_{ADA}) were estimated to be -0.18 and -0.31, respectively. Modes of the distributions were estimated as 0.25 and -1.3 for the residuals in S_{NOADA} and S_{ADA} and as, 3.8U/mL for the ADA_{MEAS} in S_{ADA}, respectively. The typical ADA_{MEAS} in S_{NOADA} was fixed to the quantification limit of the assay, 0.6 U/mL, assuming that individuals in the S_{NOADA} do not have measurable ADA. These estimates were in agreement with the expectation where i) the PK_{RES} when ADA are present would be negative (associated with model over-predictions in the presence of ADA); ii) the ADA_{MEAS} should be positive when ADA are present. Transition probabilities were low (0.089 and 0.086) for the transition from S_{NOADA} to S_{ADA}, and S_{ADA} to S_{NOADA}, respectively). Standard errors (SE) of the estimated parameters were <25% RSE with the exception of the transition probabilities (>100%). The mean time to transit to S_{ADA} was 52.8 days, while the observed mean time to clinical positivity was 60.9 days. 21.3% individuals of those that were in S_{ADA} were identified as being transient ADA producers.

Conclusions: A BV-MHMM utilizing PK_{RES} and ADA_{MEAS} in characterizing ADA formation against Cimzia was developed. The model was able to characterize the transient/persistent ADA profiles and suggested ADA positivity earlier than conventional ELISA ADA measurements assays. The results suggest that the BV-MHMM may be able to identify PK altering ADA and as such the model can be considered a relevant complement for ADA characterization in addition to assay results. This model may prove to be more promising to characterize the onset of ADA formation and to explore the impact of covariates in driving the transient/persistent ADA formation and effects on Cimzia PK. Further investigations are warranted.

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Disclosures: RLG & BL are employees of [b,c], and AB SJ, MOK, ELP of [a].

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III-30: *Philippine Eloy* Genetics of nevirapine and anti-tuberculosis drugs pharmacokinetics interaction in HIV-tuberculosis co-infected patients in Mozambique

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Objectives: Nevirapine (NVP) is a non-nucleoside reverse-transcriptase inhibitor of human immunodeficiency virus (HIV) type 1. NVP can be coadministered safely with standard anti-tuberculosis (anti-TB) treatment in coinfected patients [1]. Standard anti-TB treatment includes rifampicin (RMP), a potent cytochrome P450 (CYP) inducer, and isoniazid for 6 months with ethambutol plus pyrazinamide for the first 2 months.

NVP is metabolized mainly through CYP3A and CYP2B6 both demonstrated to be inducible and encoded in highly polymorphic genes [2]. Indeed, the *CYP2B6* G516T polymorphism has been associated with increased NVP exposure in a Cambodian population [3]. Here, we use a modelling approach to characterize the pharmacokinetics (PK) of NVP when co-administered with anti-TB drugs in TB-HIV coinfected patients in Mozambique and explore transport and metabolism genes SNP in this population.

Methods: HIV-TB coinfected patients were recruited from the CARINEMO-ANRS12146 study [4] who had consented for genetic testing to be enrolled in the CARINEMO-ANRS12214 sub-study. Anti-TB treatment (RMP, isoniazid, pyrazinamide, ethambutol) was initiated and patients were randomized 4 to 6 weeks later to receive ART based on efavirenz or NVP. Here, we focus on participants who received NVP plus two nucleoside reverse-transcriptase inhibitors.

NVP pre-dose concentration was assayed at months 1, 3, 6, (on anti-TB treatment) and 9 and 12 (off anti-TB treatment) by HPLC with a limit of quantification of 25 ng/mL [5]. Extensive PK sampling was performed in 20 participants at months 1 and 7 (sampling times: pre-dose, H0.5, H1, H1.5, H2, H4, H6, H8, H10, H12).

Plasma concentrations of NVP were analyzed using nonlinear mixed-effects software Monolix v2016R1. The structural, between-subject variability (BSV) and residual variability models were developed using the data from the month 7 extensive PK sampling, while patients were off anti-TB treatment. The between occasion variability (BOV) model was developed on months 1 and 7 extensive PK data and effect of anti-TB co-administration was investigated on these data. When including all patients at all occasions we added a second residual error variability model, specific to pre-dose concentrations, allowing more variability as dose intake was not supervised.

Genotyping for *CYP2B6*, *NAT2*, *CYP2A6*, *CYP3A4*, *CYP3A5* and *ABCB1* was performed.

Results: Among 252 patients who enrolled in NVP arm, 251 had at least 1 NVP concentration available. The number of patients with NVP pre-dose concentration available was 103, 217, 237, 229, 226 at months 1, 3, 6, 9 and 12 respectively. 20 patients enrolled in the extensive pharmacokinetic sub-study: all patients had extensive sampling while on anti-TB and among them, 16 after discontinuation of anti-TB. A 1-compatment (V/F= 69.7 L) model with one-order absorption (ka= 1.32 /h) and linear elimination (CL/F= 1.92 L/h, BSV=24%, BOV=28%) best fit the data. We used a fraction of dose absorbed parameter p fixed to 1 which

BSV= 38% captured the correlation between V and CL. Two proportional error models (s_{PK}= 2% and s_{res}= 9%) were used for concentrations from the extensive PK sub-study and the pre-dose samples respectively. Model selection was performed based on Bayesian information criterion and goodness-of-fit plots. Anti-TB treatment was shown to increase NVP apparent clearance in patients taking both NVP and anti-TB treatment by 46% ($p<10^{-10}$).

Among the 251 patients with at least 1 NVP concentration available, 146 also had at least 1 genotype available. Loss-of-function allele frequencies in our population were: *ABCB1* rs1045642 : 11% ; *CYP2B6* rs3745274 (G516T) : 43% ; *CYP2B6* rs7251950 : 7% ; *CYP2A6* rs8192726 : 94% ; *CYP3A4* rs35599367 : none ; *CYP3A5* rs776746 : 18% and 10% of participants were considered as slow NAT2 acetylators.

Conclusions: To our knowledge, this is the first study modelling NVP PK on and off anti-TB treatment and showing a significant 46% increase in NVP apparent clearance when co-administered with anti-TB drugs including RMP. Description of drug-metabolizing enzymes and transporters genes SNPs frequency in a Mozambique population is the first step before analyzing which of these genetic polymorphisms will be significant covariates of the model and how they will impact the NVP-TB drugs drug-drug interaction.

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III-31: *Hannah Britz* Physiologically-based pharmacokinetic (PBPK) modeling of the strong CYP1A2 inhibitor fluvoxamine

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Objectives: Fluvoxamine is described as a potent CYP1A2 and CYP2C19 inhibitor. The US Food and Drug Administration (FDA) recommends fluvoxamine as a perpetrator drug to evaluate the impact of CYP1A2/CYP2C19 inhibition on CYP1A2/CYP2C19 substrates (victim drugs) during co-administration [1]. The objectives of this study were to establish a whole-body PBPK model of fluvoxamine, to describe and predict the pharmacokinetics of fluvoxamine, and to apply this model for the investigation of fluvoxamine drug-gene interactions (DGIs) and drug-drug interactions (DDIs).

Methods: The whole-body fluvoxamine PBPK model was built with PK-Sim® and MoBi® (7.2.1). Drug-dependent parameters (e.g. logP, solubility), plasma concentration-time profiles (30 mg as intravenous and 10-200 mg as oral administration) and study population demographics (e.g. age, weight) of clinical studies with fluvoxamine were obtained from literature. To characterize the impact of different CYP2D6 genotypes on fluvoxamine pharmacokinetics, plasma concentration-time profiles of CYP2D6 extensive metabolizers (EMs) and CYP2D6 poor metabolizers (PMs) were included into the dataset. Model parameters that could not be obtained from literature were optimized utilizing observed plasma concentration-time profiles of fluvoxamine after intravenous and oral administration (training dataset, 10 different studies). Model evaluation was performed by prediction of plasma concentration-time profiles of studies that have not been used for parameter optimization (test dataset, 17 different studies), followed by the comparison of predicted versus observed plasma concentration-time profiles, AUC (area under the curve) values and Cmax (peak plasma concentration) values.

Results: The developed fluvoxamine model incorporates metabolism via CYP2D6 and CYP1A2 as well as glomerular filtration. The metabolic pathways were implemented with saturable Michaelis-Menten kinetics to describe the non-linear pharmacokinetics of fluvoxamine [2]. Fractions metabolized by CYP2D6 and CYP1A2 are depicted accurately. Plasma concentration-time profiles of CYP2D6 extensive metabolizers can be precisely predicted with AUC and Cmax ratios (predicted/observed) of 0.87 and 1.0, respectively. Plasma concentration-time profiles of CYP2D6 poor metabolizers can be successfully predicted with AUC and Cmax ratios (predicted/observed) of 1.28 and 1.13. The competitive inhibition of CYP1A2 by fluvoxamine was implemented and evaluated with clinical DDI data of fluvoxamine co-administration with the CYP1A2 victim drug caffeine (PK-Sim template model). During concomitant treatment with fluvoxamine, the observed AUC and Cmax of caffeine increase 13.71- and 1.40-fold [3]. The DDI model predicts a 19.48-fold increase in caffeine AUC and a 1.08-fold increase in Cmax during co-treatment with fluvoxamine.

Conclusions: The newly developed whole-body fluvoxamine PBPK model precisely describes and predicts plasma concentration-time profiles of fluvoxamine over the full range of administered doses and administration protocols. It is a valuable tool to predict the impact of CYP2D6 polymorphism on the pharmacokinetics of fluvoxamine (DGI) and to predict the impact of CYP1A2 inhibition on the pharmacokinetics of the CYP1A2 victim drug caffeine (DDI).

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III-32: *Astrid Broeker* An integrated pharmacometric dialysis model to evaluate the pharmacokinetic impact of renal replacement therapy

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Objectives: Renal replacement therapy (RRT) may alter the pharmacokinetic (PK) profile. Information on the impact of RRT on the PK is commonly obtained in small patient collectives. The aim of this project was to (i) develop an integrative, pharmacometric analysis method for PK studies in RRT in "small-n" studies, and (ii) evaluate the approach in simulation-estimation studies as well as using data from clinical trials with tigecycline and doripenem receiving continuous veno-venous haemodialysis (CVVHD) or -diafiltration (CVVHDF).

Methods: An integrated pharmacometric dialysis model was developed and implemented in NONMEM® 7.4.1, which simultaneously included all measureable dialysis specimens (plasma pre-/post filter, effluent, collected effluent). For a hypothetical drug (V: 30 L, CL: 2-3 L/h, CL_{dial}: 0.3-3 L/h), study scenarios were created and either the integrated pharmacometric dialysis model or conventional models, evaluating only one dialysis specimen at a time, were utilised in a stochastic simulation and estimation study facilitated by PsN (Version 4.7.0). Based on published information, adsorption to the dialysate membrane and drug degradation were included as potential influential factors on the measured dialysis specimens. The performance of all models was compared considering the power to detect a dialysis clearance in a small-n study (10 dialysis patients and 10 non-dialysis patients, rich sampling schedule), as well as attained accuracy, expressed as relative bias (rBias) and precision, expressed as relative root mean squared error (rRMSE) of all estimated parameters. The integrated model was applied to clinical datasets of tigecycline and doripenem.

Results: The integrated model was superior over the conventional approaches at the same total patient number: While in the plasma-pre-filter setting, a dialysis clearance had to be 60 % of the intrinsic clearance to be detectable with an 80 % power, the integrated approach was >1000-fold more sensitive and estimated dialysis clearance was unbiased (rBias: <0.2 %) and highly precise (rRMSE <2.5 %). In addition, the integrated model allowed quantifying binding to the dialysis cartridge, as well as degradation of the drug in the collected effluent without affecting accuracy and precision. In contrast, for conventional models, adsorption to the dialysis cartridge lead to significant bias in estimated dialysis clearance (-65 %) and even affected the structural PK model parameters (e.g. up to 13.5 % rBias for V). For typical dialysate collection intervals of 12 hours, degradation in the effluent caused bias of -20.4 % using the conventional approach. Instead, using the integrated model the degradation process was quantifiable (rBias 1.3 %, rRMSE 27.1 %) and dialysis clearance was estimated accurately and precisely (rBias 0.15 %, rRMSE 16.9 %). Results were confirmed in the application study with tigecycline, where plasma pre-/post filter and effluent were estimated simultaneously, and doripenem, where collected effluent was modelled as well.

Conclusions: The integrated dialysis model better exploits PK information in RRT studies than conventional approaches and was successfully applied to clinical studies with tigecycline and doripenem. Estimation of biased dialysis clearance due to adsorptive loss or drug degradation can be avoided while power, accuracy and precision of all PK parameters can be increased using the integrated pharmacometric dialysis model. Application of the approach to further studies is highly warranted to increase the information obtained from "small-n" studies in RRT.

III-33: *Jantine Brussee* Dose Individualization of CYP3A Substrates in Children: Characterization of Maturation of Intestinal and Hepatic CYP3A Activity in Children to Predict First-pass and Systemic CYP3A-mediated Metabolism

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Objectives: Our aim is to characterize the intestinal and hepatic metabolism of midazolam in children in order to predict first-pass and systemic metabolism and fraction escaping gut wall (F_g) and hepatic (F_h) metabolism as well as total bioavailability (F_{total}). The characterization of the maturation processes in gut wall and liver is essential for development of dose individualization of CYP3A substrates in children, where the relative contribution of F_g and F_h to total bioavailability varies between drugs. For this purpose, a previously developed physiological population pharmacokinetic modelling approach [1] was applied in which accepted PBPK principles and parameter values from literature are combined with the estimation of intrinsic clearance parameters based on population PK data. In this work, the estimated intrinsic clearance of midazolam is used as a surrogate marker for CYP3A activity.

Methods: Pharmacokinetic (PK) data of midazolam and 1-OH-midazolam was available from 266 post-operative children aged 1-18 years who received orally administered midazolam [2]. The physiological population PK model [1] used to analyze these data, includes physiological compartments representing the gut wall, the portal vein and the liver, and empirical central and peripheral distribution compartments for midazolam and 1-OH-midazolam. Age-specific hematocrit values and formulas for calculation of the age-specific physiological parameter values for tissue volumes, organ blood flows, intestinal surface area, and abundance of plasma proteins were obtained from literature (e.g. for liver volumes [3]). Central and peripheral volumes were linearly scaled from adults. The fraction midazolam metabolized into 1-OH-midazolam was assumed 100%. Intrinsic intestinal and hepatic clearance values were estimated based on the PK data and from these parameters, gut wall, hepatic, and total bioavailability (F_g, F_h and F_{total}) as well as systemic plasma clearance were derived. The model was evaluated using goodness-of-fit plots, bootstrap and NPDE analysis. To evaluate the assumptions made by using the physiological parameters, a sensitivity analysis was performed.

Results: The intrinsic clearance of midazolam in the gut wall and liver were found to increase with body weight throughout the pediatric age-range, but they did not mature in parallel. The exponents in the body-weight based covariate relationships were 0.98 (RSE 9%) and 0.38 (RSE 18%) for intestinal and hepatic intrinsic clearance, respectively. The intestinal intrinsic clearance proved lower than hepatic intrinsic clearance through the entire range with a 219 times lower intestinal clearance compared to hepatic clearance in children < 2 years of age, while this factor difference was 60 in children ≥ 16 years-of-age. Based on the estimated intrinsic clearance, the fraction unbound, hepatic blood flow and blood: plasma ratio, it can be derived that the systemic plasma clearance also increases with age from 9.3 L/h in infants to 24.2 L/h in adolescents. The fractions escaping gut wall (F_g) and hepatic metabolism (F_h) were derived from the estimated intrinsic clearance, the organ blood flows and the unbound drug fraction. In all children, the F_g was found to be lower (median F_g 0.36, range 0.02-0.88) than the F_h (median F_h 0.65, range 0.32-0.93). The F_h showed an increase with age, ranging from 54% in children < 2 years of age, to 70% in adolescents of 12-18 years of age, while F_g showed an inverse, but smaller, age-related trend. The resulting total

bioavailability was found to be age-independent with a median of 21.6% in children (95%CI: 3.9-51.1%). The sensitivity analysis indicated that changes in assumed values for hepatic or the intestinal blood flow would not impact the derived values for plasma clearance and bioavailability.

Conclusions: The intrinsic CYP3A-mediated gut wall clearance is substantially lower than the intrinsic hepatic CYP3A-mediated clearance throughout the pediatric age-range. Using intrinsic clearance of midazolam as surrogate marker for intestinal and hepatic CYP3A activity, gut wall CYP3A activity is less mature in young children, but matures faster than hepatic CYP3A activity. This, together with disproportional changes in blood flow, results in decreasing intestinal and increasing hepatic bioavailability with age, which together lead to little or no changes in total oral bioavailability of midazolam in children with increasing age and body weight.

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III-34: *Thierry Buclin* Closed-loop control for propofol administration during anesthesia based on real-time concentration measurement: a simulation study

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Objectives: Propofol administration through open-loop target controlled infusion (TCI) devices is largely used in clinical practice to induce and maintain both sedation and general anesthesia. The classic TCI algorithm adjusts drug infusion rates to rapidly achieve and preserve stable brain concentrations according to model-predicted plasma and brain levels [1]. The pharmacokinetic (PK) model currently in use in most hospitals was developed on a small set of volunteers [2]. However, an important between-subject variability (BSV) characterizes propofol PK in clinical conditions [3]. This implies that actual propofol levels differ from predicted ones in a significant fraction of patients, so that current TCI pumps deliver inadequate drug dosages with possible important consequences for the patients [4]. Closed-loop automated anesthesia delivery systems might clearly improve the safety and the quality of anesthesia care while giving the anesthesiologists the opportunity to focus on the higher-level clinical tasks required during the surgery [5]. We participate in a project aiming at developing a miniaturized sensor able to monitor circulating propofol during surgery [6]. The aim of the present work was to develop a closed-loop algorithm for propofol administration driven by real-time plasma measurements and to evaluate its performances through a simulation study.

Methods: The suggested algorithm couples the Bayesian minimization approach with the classic open TCI algorithm of Shafer *et al.* Study population consisted of 1000 simulated female subjects (70 kg, 170 cm, 36 y) with *real* PK parameters obtained by the comprehensive model of Eleveld *et al* with BSV [3]. Bayesian minimization of the Eleveld *et al* model based on all the real-time plasma measurements up to the last available one allowed personalizing the population microconstants of the classic TCI algorithm, so to predict each individual brain concentration-time profile. Plasma measurements were generated using the *real* individual PK parameters, the model intraindividual variability, and the computed infusion rates. A constant brain target concentration of 5 mg/L (accepted surfaces: target +/-30% (large criterion, LC), 20% (average, AC) or 10% (strict, SC) of target) over a 60 min surgery was chosen. The number of subjects achieving the target surface was calculated. In addition, we defined as *problematic* patients those reaching the target surface more than 20 min after operation started, spent less than 20 min in the target surface or had average concentration outside the target surface longer than 5 min. Percentages of *problematic* individuals receiving propofol at infusion rates computed by classic TCI and our closed-loop algorithm were compared. The proposed approach was evaluated against measurement period (step=15 and 60 sec) and delay between real time blood sampling and arrival time for data processing (35 sec) according to the characteristics of the existing sensor prototype for continuous propofol quantification [6]. For the highest step, the role of the proportional component of the intraindividual variability was explored (model: 47%, tested: 24%).

Results: Target was achieved in 99% (LC), 95% (AC) and 86% (SC) of the subjects with 25%, 47% and 78% identified as *problematic* for classic TCI administration. Conversely, all the patients reached the target when computing infusion rates with the proposed approach independently of the chosen period and delay. Moreover, only problematic according to LC and AC for step=60 sec including or not the delay. The percentage of SC *problematic* patients increases from 27% to 31% and from 73% to 76% for step=15 and 60

sec, respectively, upon integration of delay in the closed-loop algorithm. As expected, lowering the proportional component of the intraindividual variability decreased the number of *problematic* patients for step=60 sec to <2% for LC and AC and <44% for SC independently of the delay.

Conclusions: The suggested closed-loop algorithm based on real-time plasma measurement markedly reduces the number of patients significantly under- or over-exposed during anesthesia relatively to the classic TCI devices. Measurement delay minimally affects the performances of the approach, which not surprisingly depends on measurement period and noise.

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III-35: *Wonkyung Byon* Apixaban for treatment of venous thromboembolism (VTEtx): Use of Model-Based Meta-Analysis (MBMA) to support Phase 3 dose selection and beyond

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Objectives:

Apixaban is an orally available, direct, selective inhibitor of the coagulation factor Xa that reversibly binds to the active site of FXa, and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. Apixaban is approved in multiple regions for VTEtx, based on the results of a Phase 3 study (AMPLIFY [1]). Model-Based Meta-Analyses (MBMA) can inform drug development decisions and increase the probability of technical success. Here we describe how the results of MBMA were used to support dose selection for the Phase 3 VTEtx study of apixaban (apixaban 10 mg twice daily [BID] for 7 days, followed by 5 mg BID in AMPLIFY) and how the models were updated and used during the conduct of the study to address questions and inform decisions.

Methods: Efficacy and safety dose-response data from 20 treatments evaluated in the prevention of VTE (VTEp) following orthopedic surgery (representing > 39,000 patients in 63 trials) were fit with logistic regression models that specified a similar shape of the dose-response (D-R) curve across compounds [2].D-R MBMA of total VTE and major bleeding (MB) for anticoagulants in VTEp were linked to efficacy (symptomatic VTE) and safety (MB) in VTEtx to generate D-R relationships across compounds, with doses expressed as enoxaparin equivalents. Separate relationships were determined for acute (5-14 days) and chronic (>14 days up to 6 months) effects of the initial treatment. Using these models, VTE and MB event frequencies for various dose regimens of apixaban were estimated. As additional clinical trial data became available for both VTEp and VTEtx during the conduct of the AMPLIFY trial, the models and expected outcomes were updated and used, along with blinded event rates, to assess the impact of an increase in sample size using clinical trial simulations, as well as any impact on hierarchical statistical testing.

Results: An apixaban regimen of 10 mg BID for 7 days followed by 5 mg BID was predicted to result in similar or better efficacy and safety vs. standard of care (subcutaneous enoxaparin followed by vitamin K antagonist) for the total treatment period as the model supported the benefit of a higher dose during the acute treatment period. The updated original MBMA predicted a high probability of meeting the primary objective of non-inferior efficacy of apixaban relative to enoxaparin/warfarin, but only ~50% probability of achieving superiority on efficacy with the pre-specified maximum sample size of 5400. A new network MBMA using apixaban data from the AMPLIFY-Extension study [3] was used to refine the probabilities of efficacy and bleeding outcomes in the AMPLIFY study. The probability of achieving superiority for MB was estimated to be greater than that for recurrent VTE. Based on this result, the order of hierarchical testing in the AMPLIFY study was pre-specified in the statistical analysis plan prior to the database lock, to be 1) non-inferiority for VTE, 2) superiority for MB, and 3) superiority for VTE.

Conclusions: The MBMA supported selection of a dose of 10 mg BID for 7 days followed by 5 mg BID for the 6-month treatment of VTE. In AMPLIFY, consistent with the model-based predictions, this regimen of apixaban was non-inferior for VTE and superior for MB, with observed relative risk (95% CI) of 0.84 (0.60-1.18) and 0.31 (0.17-0.55), respectively [1].

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III-36: *Tim Cardilin* Modeling of radiation therapy and radiosensitizing agents in tumor xenografts

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Objectives: To conceptually and mathematically describe the treatment effects of radiation and radiosensitizing agents on tumor volume in xenografts with respect to short- and long-term effects.

Methods: Data were generated in FaDu xenograft mouse models, where animals were treated with radiation given either as monotherapy (2 Gy per dose) or together with an early-discovery radiosensitizing agent (25 or 100 mg/kg per dose) that interferes with the repair of the DNA damage induced by irradiation. Animals received treatment following a clinically-relevant administration schedule with doses five days a week for six weeks. Tumor diameters were measured by caliper twice a week for up to 140 days. A pharmacodynamic tumor model was adapted from a previously-published model [1,2]. The improved model captures both short- and long-term treatment effects including tumor eradication and tumor regrowth. Short-term radiation effects are described by allowing lethally irradiated cells up to one more cell division before apoptosis. Long-term radiation effects are described by an irreversible decrease in tumor growth rate. The radiosensitizing agent was assumed to stimulate both processes. The model also includes a natural death rate of cancer cells. The model was calibrated to the xenograft data using a mixed-effects approach based on the FOCE method that was implemented in Mathematica [3]. Between-subject variability was accounted for in initial tumor volume, as well as in the short- and long-term radiation effects.

Results: Data across all treatment groups were well-described by the model. All model parameters were estimated with acceptable precision and biologically reasonable values. Vehicle growth was approximately exponential during the observed time period with an estimated tumor doubling time of approximately 5 days. Tumor growth following radiation therapy resulted in significant tumor regression followed by either tumor eradication (2 animals) or slow regrowth (7 animals). The short- and long-term effects incorporated into the tumor model were able to account for both of these scenarios. A simple analysis shows that if the tumor growth rate is decreased below the natural death rate, the tumor will be eradicated. Otherwise, the tumor will regrow but at a slower rate compared to pre-treatment. The model predicts that each fraction of radiation (2 Gy) results in lethal damage in 15 % of viable cells, and that a total dose above 120 Gy will eradicate the tumor. Tumor growth following combination therapy with a lower dose (25 mg/kg) resulted in more cases of tumor eradication (6 animals) and fewer cases of regrowth (3 animals), whereas combination therapy with the higher dose (100 mg/kg) resulted in tumor eradication in all 9 animals. When radiation therapy was complemented by radiosensitizing treatment (100 mg/kg per dose), each fraction of 2 Gy was estimated to kill 25 % of viable cells, and the total radiation dose required for tumor eradication was decreased by a factor four to 30 Gy.

Conclusions: A tumor model has been developed to describe the treatment effects of radiation therapy, as well as combination therapies involving radiation, in tumor xenografts. The model distinguishes between short- and long-term effects of radiation treatment and can describe different tumor dynamics, including tumor eradication and tumor regrowth at different rates. The novel tumor model can be used to predict

treatment outcomes for a broad range of treatments including radiation therapy and combination therapies with different radiosensitizing agents.

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III-37: *Evelina Cardoso* Population pharmacokinetic analysis of erlotinib in cancer patients affected by NSCLC

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Objectives: Erlotinib is an oral first-generation EGFR tyrosine kinase inhibitor approved in patients with non-small cell lung cancers (NSCLC) with EGFR activating mutations. Erlotinib is currently prescribed at fixed regimen of 150 mg once daily, and dose adjustments are proposed in case of severe acute toxicity. However, a large inter-variability in its pharmacokinetics was observed [1], which could explain the variability of clinical response (effect/toxicity). In particular, elderly patients are more subject to severe toxicities compared with younger patients [2, 3]. The aims of this study were to describe the pharmacokinetic profile of erlotinib in NSCLC patients, to identify influencing factors and to evaluate the risk of suboptimal exposure under standard dosage regimen, with a special focus on elderly patients.

Methods: Multi-compartment models were compared to characterize erlotinib pharmacokinetics (PK) (NONMEM®). The effect of relevant covariates (age, sex, body weight, body mass index, smoking status, albumin, AST/ALT, C-reactive protein [CRP], sarcopenia, moderate/strong CYP3A4 inhibitors [INHM3A4, INHP3A4] and inducers [INDM3A4, INDP3A4], moderate CYP1A2 inhibitors/inducers [INHM1A2, INDM1A2], strong CYP1A2 inhibitors [INHP1A2], strong P-glycoprotein inhibitors/inducers [INHPPGP/ INDPPGP], Proton Pump inhibitors [PPI]) was explored using linear equations. The adequacy of the recommended dosage regimen (150 mg/day) was assessed in several age group through simulations in 1000 individuals based on the final model with inter-patient variability. Erlotinib minimal concentrations (C_{min}) > 2000 ng/ml was used as the upper limit defining overexposure and potential toxicity [3]. The percentage of patients in each age category reaching this upper limit target was calculated after administration of standard and alternative dosage regimens.

Results: The study population included a total of 482 erlotinib plasma concentrations collected from 91 cancer patients (25-91 years old) as part as a routine therapeutic drug monitoring program at the Cochin Hospital. A one-compartment model with first-order absorption and elimination provided the best model fit of erlotinib PK. Apparent clearance (CL/F) was 3.8 L/h (IIV, %CV 39%) and the apparent volume of distribution (V/F) was 165 L (%CV 47%). The absorption rate constant was 1.41 h^{-1} (RSE 24%). Univariate analyses revealed a significant relationship between erlotinib CL/F and age, smoking, albumin, CRP, dual INHM3A4 and INHM1A2, moderate or strong IND3A4, INHPPGP, INDPPGP and PPI ($p<0.05$). Multivariate analyses with stepwise inclusion ($p<0.05$) and backward deletion ($p<0.01$) identified an increase of erlotinib CL/F in smokers by 44% and in presence of PPI (36%) or following the intake of an IND3A4 (69%). ALBU also increase CL/F by 7% when ALBU=36 (25th percentile, P25) compared to ALBU=41 (P75). In contrary, in presence of a dual INHM3A4 and INHM1A2, erlotinib CL/F decrease by 43%. Age was associated with a decrease in CL/F of 19% in 76 years old (P75) compared to 59 years old (P25) patients. The model-based simulations show that under 150mg daily, the percentage of patients with C_{min} > 2000 ng/ml is 9% at 40 and increase to 15% at 60, 22% at 70 and 28% at 80 years old. Reducing the dose from 150 mg to 100 mg for 70 years old patients or older would decrease the risk of overexposure.

Conclusions: This study confirm the large variability in erlotinib pharmacokinetics and the large influence of smoking and PPI intake on drug concentrations. As expected, medications modulating CYP3A4 and CYP1A2 activity modify erlotinib concentrations, which might lead to suboptimal exposure. Erlotinib CL decreases with age, increasing the risk of C_{min} > 2000 ng/ml, which could explain the greater toxicity and more

frequent discontinuation observed in elderly patients. A lower starting dose could be considered in this at risk population while accounting for the additive effect of co-medications and efficacy endpoints.

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III-38: *Marc Cerou* HAM-D score analysis of patients under placebo with major depressive disorder using item response theory

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Objectives: Item Response Theory (IRT) is increasingly used in Pharmacometrics to model the disease progression using the whole available item-level information [1]. As a first step, our aim was to analyze and evaluate the time course of response to placebo of patients with major depressive disorder using this approach.

Methods:

Data

The dataset includes 2136 patients where we had longitudinal observation for 626 patients under placebo and information at baseline for 1510 patients in the treatment arm. The data was collected from one phase II and seven phase III clinical studies where the tested drug was Agomelatine, which was marketed in 2009. At each observation time, item information of the Hamilton depression rating scale (HAM-D) [2] which contains 17 items was collected. The number of visits by patient ranges from 3 to 42 (9 in median) and the follow-up period was 14 days in median. Study duration was decomposed as one short term study (2 months), five midterm studies (6 months), and two long term studies (12 months) and the number of patients among studies was very similar (around 120). Dropout information in the studies was recorded and the causes were mainly due to lack of effect, adverse event or at random. Approximately 60% of patients dropped out in a year.

HAM-D IRT model

The first step was to estimate the item-specific parameters, implemented as fixed effect of ordered categorical models and latent depression disability as random effect and for that purpose we used all available information.

Longitudinal model

The second step was to estimate the evolution of the hidden depression disability over time by fixing the item-specific parameters and using several mixed-effect models.

Longitudinal model with dropout

To take into account the dropout, we used a time-to-event (TTE) parametric model and several distributions of the baseline hazard model were tested. To characterise the relationship between dropout and the latent depression disability (LDD), several forms of link were explored.

Model selection and evaluation

Model selection was done based on the AIC. Model evaluation was done through graphical diagnostics based on both item and summary levels (mirror plot) and also to Visual predictive check (VPC) based on the HAM-D score. VPC of Kaplan-Meier was computed to evaluate the dropout model. The best model was selected on the basis of all these numerical and graphical diagnostics, but also on uncertainty of the parameters, a relevant interpretation of the parameters and a clinically pertinent model.

Results:

HAM-D IRT model

A total of 92 parameters was estimated with 10 ordinal categorical sub-models of 5 scores, and 8 ordinal categorical sub-models of 3 scores. The mirror plot and summary level checks showed good agreement with observations.

Longitudinal model

Depression time course based on the HAMD corresponds to a strong diminution (remission) and it can be associated with a relapse. Several models were tested: linear (AIC: 197655), Weibull [3] (AIC: 188348), Bateman [4] (AIC: 189045), a modified inverse Bateman (AIC: 188277) and a second modified inverse Bateman (AIC: 188519). Based on AIC and the graphical diagnostics, the model of the latent depression disability which best described the data was the first modified Bateman model, where the shape of the diminution corresponds to a Weibull like model.

Joint model with longitudinal and TTE sub-models

Patients with high value of LDD were strongly associated with a dropout. A Weibull model for the hazard was tested and several forms of link were explored: no link (AIC: 138073), link with the current value of the LDD (AIC: 137711), link with a logit transformation of the current value of the LDD (AIC: 138714). A lognormal model for the hazard with a link with the current value of the LDD was also tested (AIC: 138895). Based on numerical and graphical diagnostics, the selected model was a Weibull model for the hazard with a link with the current value of the LDD. The relative standard error for this model was under 5% for all parameters, and VPC of the HAMD-D score was in good agreement with the observations.

Conclusion:

A longitudinal IRT model has been developed and is a suitable method to describe the disease progression of depressed patients. This model will be used and adapted to take into account treatment effect. This work could be used later as a basis for the study of the normalised prediction distribution errors, a metric used in model evaluation, adapted to this type of data.

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III-39: *Blesson Chacko* Covariate effects on competing events: a simulation study comparing approaches

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Objectives: To compare the performance of various analysis methods to detect covariate effects on competing events. To explore the influence of sample size. To visualise model predictions versus observations.

Methods: 200 studies were repeatedly simulated while varying sample size (100 to 1000), intensity and direction of binary covariate influence on event of interest (response) and on competing event (dropout) with right censoring at a fixed cut-off time. The two competing events (response and dropout) were simulated using the same exponential hazard function.

The covariate effect on the response rate and on the individual response risk was investigated in all the simulated studies by the cause-specific hazard (CSH) and by the sub-distribution hazard (SDH), respectively. Covariate effects on the cumulative incidence of the events (cause-specific cumulative incidence function, CSCIF and sub-distribution cumulative incidence function, SDCIF) were visualised by indirectly calculating the CSCIF or by directly modelling the SDCIF.

Covariate effects on the CSH were analysed either by the semi-parametric Cox proportional hazard (PH) model or by parametric CSH modelling using exponential hazard functions. Covariate effects on the SDH were analysed with the semi-parametric Fine-Gray method [1] or by directly modelling the SDCIF with a modified three-parameter logistic hazard function and a generalised odds-rate link function under the constraint that the asymptotes of SDCIFs for the competing events must add up to one [2]. The utility of various link functions was explored.

Results: The type I and type II error (power) of detecting the true covariate effect on the response were calculated for various analysis methods. The performance of the Cox PH model and the parametric CSH model was similar and the 'blind spot' was found in the expected location where 'no covariate effect on the response rate' was true. The simultaneous covariate effect on the dropout rate was not tested with CSH. Statistical power increased, as expected, when the sample size was increased. Modelling the CSH alone did not identify a covariate effect on the individual response risk, and the covariate effect on the dropout remained unidentified due to the treatment of dropout as right-censoring. In contrast, the Fine-Gray model analysed the covariate effect on the individual risk of a response while taking the simultaneous risk of dropout into account. It provided a visualisation of the covariate effect on the SDCIF of the response. The 'blind spot' of this method lay where the covariate effect on the risk of response and dropout were equally strong. Similar performance was obtained by the direct parametric modelling of SDCIF with the generalised odds-rate link function fixed to mimic the proportional hazard (log-minus-log) model for regression (used also in the Fine-Gray model). Changing the parameter of the generalised odds-rate link function, however, showed that log-minus-log was not always the best model according to the Akaike information criterion (AIC). Therefore, the directly modelled SDCIF might fail to correctly estimate the covariate effect on the response risk when the SDCIF was poorly approximated. Visualisations of the SDCIF helped in model-building.

Conclusions: Covariate effects on the response rate, identified by the Cox PH model, describe the underlying aetiology and are not suited for predicting the covariate influence on future individual risks. No advantage is gained by parametric modelling of the CSH. This conclusion extends to most parametric time-to-event modelling presented at recent pharmacometric meetings. To identify individual risks in a situation of competing events (only two were simulated here, but the methods can handle any number) the SDH needs to be modelled. The semi-parametric Fine-Gray method is well established; a direct parametric modelling of the SDCIF qualifies the proportional hazard model or proposes useful alternatives. It also affords clear visualisation of the covariate effects in the presence of competing events similar to the standard visual predictive checks. Still, also the SDH models have their 'blind spot' where the covariate effect on the competing events is equal. For a comprehensive analysis of covariate effects on competing events, separate CSH models for each competing event and SDH models for the combined events are needed. With these models in place, future studies can be designed and powered adequately.

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III-40: *Dong Woo Chae* Predictive Modeling of PCA Effect on Postoperative Pain Management

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Objectives:

Our study aims to develop predictive models of the time course of postoperative pain and nausea under patient controlled analgesia (PCA) treatment.

Methods:

Serial postoperative visual analogue scale (VAS) pain scores and severity of nausea scale (N) ranging from 1 to 10 of 28,656 patients were retrospectively collected. The typical time course of VAS is characterized by an initial surge of pain severity due to diminishing post-anesthetic effect followed by an eventual pain relief. A0, Kane, Kon, and Emax denote the percentage reduction of VAS relative to 10 at baseline, rate constant of disappearance of post-anesthetic effect, rate constant of pain relief, and the maximal percentage reduction of VAS. Covariate search was carried out to identify factors affecting the model parameters. Basal infusion rate was tested for its effect on Kon and Emax. N was described as a sum of two surge functions, each representing the early nausea occurrence due to surgical procedures and post-anesthetic effect and delayed nausea development due to PCA exposure. Covariates that significanly increased the probability of nausea occurrence were identified. The final VAS and nausea models were fitted using a training dataset consisting of 10,000 patients and validated using two test datasets each consisting of 10,000 and 8,656 patients.

Results:

General and spinal anesthesia showed distinct pain profiles with the latter characterized by a lower baseline VAS. In IV PCA patients, typical A0 estimates of general and spinal anesthesia were 60% and 90%, respectively, with similar values of 60% and 92% in epidural PCA patients. Kon was lower in epidural PCA compared to IV and PCA patients, with typical values of 0.087/h and 0.12/h, respectively. Emax was higher in IV PCA patients, with its typical estimate of 75% compared to 69% in epidural PCA patients. Younger age was significantly associated with higher A0, Kon, and Emax. Female gender was associated with lower Kon and Emax. In IV PCA patients, longer duration of anesthesia was associated with lower A0, Kon, and Emax. Higher basal infusion rate was positively correlated with Kon (IV PCA) and Emax (epidural PCA), suggestive of an analgesic dose-effect relationship. Female gender, older age, increased prescription frequencies of Keromin, Tridol, and Pethidine were associated with higher risk of nausea in both IV and epidural PCA patients. Higher basal infusion rate of PCA regimen was associated with a higher risk of nausea in IV PCA patients. The developed model was successfully validated using the test datasets.

Conclusions:

Our model successfully predicted the time courses of VAS and N under PCA infusion. The developed model would be useful in devising individualized PCA regimens under widely different situations to optimize pain and side effects management.

III-41: *Anne Chain* Extension of population pharmacokinetic analysis of pembrolizumab to paediatric patients patients with classical Hodgkin lymphoma

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Introduction: Pembrolizumab is globally approved in adults with various solid tumor as well as hematological cancer indications. To date, it is also approved in paediatric patients with classical Hodgkin lymphoma (cHL) and microsatellite instability high (MSI-H) cancers. A pooled population pharmacokinetic (PK) analysis was initially conducted using data from adults with different types of caner. Subsequently, this was extended to include PK data from paediatric patients. The current work summarizes the PK analysis including paediatric subjects to guide the dosing recommendation in patients < 18 years old with cHL.

Objectives:

- Describe the PK analysis in paediatric patients
- Assess the impact of covariates such as cancer indication, age and body weight of pembrolizumab pharmacokinetics
- Summarize simulation results supporting the recommended dosing regimens in paediatric patients

Methods: The present analysis was built on an existing population PK model in patients with melanoma or NSCLC for pembrolizumab as described in [1]. Pharmacokinetic data from paediatric patients (N=34) as well as adult cHL patients (N=229)were added to the dataset. As a first step the parameters from the existing model (including covariate effects) were re-estimated. Subsequently, potential refinements to the model were explored, with a focus on an optimal characterization of the potential effects of age and body weight in the paediatric population.

Reliability and robustness of the subsequent final model was assessed by a range of goodness of fit plots. Posthoc parameter estimates from the final model were used to compare pharmacokinetic parameters between paediatric and adult populations. Due to the limited number of patients available from the pembrolizumab paediatric study, simulation dataset was augmented with additional data (demographic / covariate information from 171 subjects) from another oncology program. Simulations from the final model were performed to assess the exposure of pembrolizumab in paediatric patients at the recommended dosing regimens of 2 mg/kg Q3W or 200 mg Q3W by age-group including adults.

Results: Overall, the updated model was generally consistent with the previously developed model [1] in terms of model structure and parameter estimates, showing a lack of clinically meaningful impact of the inclusion of data from paediatric and cHL studies. In addition to the effects of body weight on pembrolizumab pharmacokinetic parameters as incorporated in the existing model, an effect of age was also found within the paediatric subgroup, resulting in decreasing clearance and central volume of distribution with decreasing age.

Despite clear effects of lower body weight on clearance and volume of distribution in the youngest age groups, no major differences were apparent between these populations in terms of exposure parameters (AUC, Cmin, Cmax). Simulation results of exposures in paediatric patients down to age of 6 years demonstrated that predicted exposures at 2 mg/kg Q3W for 6-12 years old patients are similar to

adolescents and adults administered with 200 mg Q3W. In the group of 2-6 years old, predicted exposures at 2 mg/kg Q3W are ~30% higher than in adults.

Conclusion:

- Inclusion of PK data from the paediatric and cHL studies do not lead to any meaningful change in the parameter estimates of the population PK model for pembrolizumab.
- Within the paediatric population, lower age is associated with lower clearance and volume of distribution.
- The weight based dosing regimen of 2 mg/kg Q3W assures similar pembrolizumab exposures across different paediatric age groups down to 6 years and in comparison to adults. In 2-6 years old, exposure to pembrolizumab is ~30% higher in comparison to adults. In

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III-42: *Pascal Chanu* Pediatric plans optimization of C.E.R.A. (Continuous Erythropoietin Receptor Activator): clinical evidence obtained through a model-based integration of multisource data

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Objectives:

C.E.R.A. indicated in Chronic Kidney Disease (CKD) patients (pts) to correct and maintain hemoglobin (Hb) levels has been approved in Europe and US in 2007 in adults. Roche also submitted Pediatric Investigation and Pediatric Study Plans for C.E.R.A. As part of the pediatric development plans, a 20-week open-label Phase II study (NH19707) of intravenous (IV) C.E.R.A. in pts aged 5–17 years was conducted. In pediatric patients, the goal is to maintain Hb levels with C.E.R.A. after correction by another Erythropoietin Stimulating Agent. The data collected in this trial was analysed with adult IV and subcutaneous (SC) data. The objectives were to determine the PK/PD characteristics of C.E.R.A. in a broad population and, using simulations, to optimize the design of a second pediatric study using SC administration of C.E.R.A.

Methods:

PK and Hb data from 63 pediatric pts were pooled with 400 pts adult IV and SC data. Adult PK/PD structural models previously developed were used for the analyses[1]. A non-linear mixed effect modeling approach was applied. Assumptions on C.E.R.A. SC bioavailability in pediatric patients were based on darbepoetin data[2,3]. Simulations tested various values of bioavailability. Model inferences were challenged versus Real World Data (RWD) from registries maintained by the International Pediatric Dialysis Network (IPDN, www.pedpd.org). RWD were obtained in 107 pediatric patients receiving C.E.R.A. SC and 22 pediatric patients receiving C.E.R.A. IV.

Results:

The adult PK model (1-compartment model with first order absorption and elimination) adequately described the pediatric data. As in adults, C.E.R.A. clearance increased with body weight and the volume of distribution increased with body weight and age. Once those body-size related covariates were accounted for, there was no difference in PK between adult and pediatric pts. The PK/PD model developed on adult data could be successfully applied to pediatric data. The drug dependent parameters were comparable in pediatric and adult pts indicating a similar exposure-response relationship in both populations. The SC study design was simulated assuming a reduced number of subjects (N=25) compared to the one foreseen in existing pediatric plans (N=150). The different scenarios tested either no increase or 30% to 50% increase in bioavailability in pediatric patients compared to adults. Results are presented in Table 1 and showed that prediction intervals of the mean change of Hb from baseline included the value 0.

Table 1: Simulations of Hb and Dose Distribution at the End of Evaluation Period (Week 20)

Scenarios	SC simulations	Observations (SC) from IPDN	IV simulations	Observations (IV) from NH19707
	Mean change in Hb from baseline (g/dL) and 95% prediction interval			
F	-0.26 [-1.39;0.80]	IPDN: NA	0.07 [-0.22;0.43]	NH19707: -0.09
1.3F	-0.14 [-1.47;0.82]			
1.5F	0.04 [-1.07;1.05]			
	Mean Hb (g/dL) and 95% prediction interval			
F	10.80 [10.36;11.26]	IPDN: 10.9	10.95 [10.57;11.31]	NH19707: 10.94
1.3F	10.88 [10.49;11.26]			
1.5F	10.92 [10.46;11.34]			
	Median dose[a] (µg every 4 weeks) and 95% prediction interval			
F	125 [81;220]	IPDN: 100	84 [60,123]	NH19707: 120
1.3F	110 [73;184]			
1.5F	101 [60;170]			

F: assuming adult bioavailability, 1.3F and 1.5F: assuming 30% and 50% increase in bioavailaility respectively compared to adults

a: C.E.R.A. doses are adjusted according to Hb levels

Previous data on darbepoetin suggested that the most likely scenario is a 50% increase in bioavailability compared to adults. RWD confirmed model predictions as shown in Table 1. Additional safety information was obtained from the literature[4,5]. Revised pediatric plans were approved by FDA and EMA.

Conclusions:

The PK/PD characteristics of C.E.R.A. are similar between adult and pediatric populations. Simulations of clinical outcomes support pediatric plans optimization with reduced costs, time and burden to patients while maximizing information on the target pediatric population; and support C.E.R.A. IV and SC dosing in pediatric pts with CKD.

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III-43: *Estelle Chasseloup* Generation and Application of Avatars (Digital Twins) in Pharmacometric Modelling

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Objectives: The concept of Avatars or Digital Twins is well established in health, engineering, and systems biology. It is the creation of a digital representation of a physical or a biological system in order to explore and control its behaviour [1,2]. In this work we aim to explore aspects of generating and utilizing avatars for pharmacometric population models, accounting for clinical relevance. We used a neutropenia model as example.

Methods: A previously published pharmacodynamic model describing the neutrophil count after a single administration of docetaxel and its associated database (3553 observations for 601 IDs) were used [3]. In oncology the main clinical endpoints to monitor the haematological toxicities after a chemotherapy treatment are the count of the white blood cells before treatment (at baseline, B), at maximal depletion (nadir, N), and at the expected time of the next dose (return, R). The avatars were selected among model simulations according to the closeness of the simulated individuals to these clinically relevant criteria. All the combinations of these three clinical endpoints were tested (e.g. N, BN, and BNR). The closeness was defined at the individual level as an error margin (10, 20, 30 or 50%) around the observed data values for the three clinically relevant time points. To ensure at least one avatar for each ID for the different combinations tested we varied the number of simulations (1000 or 10000). NONMEM v7.3.0 and R v3.3.0 were used for the simulations and the selection process respectively.

Results and discussion: In this work we defined avatars for population models as a subset of simulated individuals based on their closeness w.r.t the observations at clinically relevant criteria. White blood cell count vs. time profile plots show that the avatars profiles are closer to the individual observations than the whole of the simulations. Bivariate plots of the random inter-individual parameters show significant differences between the avatars, the EBEs and the estimated theoretical distributions. We also show that 10000 simulations were not enough to guarantee an avatar for each ID for stringent (10%) or less stringent (50%) error margins. The avatar properties could be interesting in different areas of pharmacometrics, e.g. refined clinical trial simulations, quantifying individual predictive performance for model based dose adjustment in clinical practice, measurement of subject uniqueness, as a model diagnostic, and coherence of the simulations with the model and not only one but multiple observed variables.

Conclusions: An efficient method to select clinically relevant avatars for population models was implemented. Avatars can give nuanced information regarding the ability of a model to simulate data similar to the observed data. A dynamic avatar selection instead of a static one (i.e. after all the simulations were done) used in this work would guarantee an avatar for each subject, even for stringent criteria, using less simulation resources. Avatars properties could then be investigated in different areas of pharmacometrics.

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III-44: *Jonathan Chauvin* COSSAC (COnditional Sampling use for Stepwise Approach based on Correlation tests) method for covariate search

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Introduction/Objectives: Covariate search is a key element in the modeling process. As it involves a large number of runs, automatic covariate search procedures have been developed. The most commonly used method is SCM (stepwise covariate modeling [1]). The SCM procedure includes a forward selection, in which covariates are added one by one after evaluation of all possible additions, followed by a backward elimination. This method is effective but expensive in terms of number of runs. We propose an alternative method called COSSAC based on the individual parameter-covariate correlations observed in the current model. The method is available as an R script to be used with MonolixSuite2018R1.

Methods: The proposed method makes use of the information contained in the base model run to choose which covariate to try first (instead of trying all covariates "blindly"). Indeed, the correlation between the individual parameters (or random effects) and the covariates hints at possibly relevant parameter-covariate relationships. If the EBEs (empirical Bayes estimates) are used (as proposed in [2]), shrinkage may bias the result. We instead propose to use samples from the a posteriori conditional distribution ([3], available as "conditional distribution" task in MonolixSuite2018R1) to calculate the correlation between the random effects and covariates. A p-value can be derived using the Pearson's correlation test for continuous covariate and ANOVA for categorical covariate. The p-values are used to sort all the random effect-covariate relationships. Relationships with the lowest p-value can be added first, run and confirmed using the classical likelihood ratio test. The precise procedure is the following:

Initialization:

- Run the base model (population parameter estimation, conditional distribution sampling, and log-likelihood estimation)
- Calculate the p-values of all the parameter-covariate relationships using Pearson's correlation tests and ANOVA (done automatically in MonolixSuite2018R1)

Forward selection:

1. Add the covariate with the smallest p-value (among the remaining parameter-covariate relationships) to the model
2. Run the model
3. Accept/reject the relationship based on the likelihood ratio test
4. Go back to step 1 until no significant p-values remain

Backward selection: same methodology as the forward step but sorting the p-value (of the correlation between the covariate and the parameter (not the random effect)) from the highest to the lowest

Results: This methodology was tested using MonolixSuite2018R1 and compared to the classical Stepwise Covariate Model (SCM) building on two examples:

- A densely sampled PK data set for remifentanil [4]. Remifentanil is an opioid analgesic drug among other used for sedation. Its PK can be modeled by a 3 compartment model (6 population parameters). The data set contains 6 correlated covariates.
- A time-to-event data set of survival for lung cancer [5]. The data is modeled with a Gompertz model (2 population parameter) and the data set contains 5 covariates.

For both strategies, log-likelihood ratio test is used to accept or reject the parameter-covariate relationship. The inclusion and exclusion criteria on the p-value are set at 0.1 and 0.05 respectively. The criteria to test the inclusion of a covariate in the proposed procedure is 4 times higher than the inclusion criteria (i.e 0.4).

For both data sets, we obtain the same final model using either the SCM and the hereby proposed procedure. However the total number of runs is much lower using the proposed algorithm:

- On the remifentanil projects (36 possible relationships), the proposed algorithm needs 32 runs, while the SCM algorithm needs 246.
- On the lung cancer event project (10 possible relationships), the proposed algorithm needs 15 runs, while the SCM algorithm needs 51.

Conclusions: We propose an efficient covariate search procedure based on the Pearson's correlation test between individual parameters randomly drawn from the conditional distribution and the covariates. Instead of comparing all parameter-covariate relationships, we test in priority the relationships with the most relevant correlation. This greatly shortens the total number of runs needed and opens the way to the selection of covariates from large covariates lists (such as genomic information).

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III-45: *Ng Chee* Novel Multilevel Parallel Expectation Maximization (MPEM) Estimation Methods for Population Quantitative Pharmacology Analysis

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Objectives: Two levels of parallelization can be used to accelerate the performance of the parametric expectation-maximization (EM) estimation methods in population quantitative pharmacology (PQP) analysis [1]. First, conditional mean (**μ**) and variance (**B**) of individual subject in the computational intensive E-step is determined independently using different computing nodes (Level 1) [2]. All parametric EM methods in the commercial PQP software (NONMEM and Phoenix) used the Level 1 parallelization (L1P). The limitations of the L1P become apparent for complex PQP analysis as solving a large system of ordinary differential equations (ODEs) with thousands of simulated random model parameters sets (ISAMPLE) for **μ** and **B** is extremely computational and time intensive. Even for simple PQP models, computing E-step with large number of ISAMPLE to achieve consistent objective function for model selection can become rate-limiting step of the EM algorithm [3]. Level 2 parallelization (L2P) can alleviate these problems by further parallelizing the L1P task within the same subject but has never been implemented and tested in parametric EM methods. In this study, we developed the **first** novel MEPM with dual parallelization levels to optimize the parallel efficiency of parametric EM methods in PQP analysis.

Methods: A MPEM method based on Monte-Carlo Parametric EM algorithm facilitated by Maximum a Posterior (MCPEM-MAP) was developed and written in C programming language. Two levels of parallelization were implemented as follows:
Level 1 – The determination of **μ** and **B** for all subjects in the E-step was divided and computed independently as parallel computing tasks (L1P).
Level 2 – A large ISAMPLE was needed to compute the likelihood for μ and B determination in each subject. Therefore, under each L1P task, further parallelization was applied to compute the likelihood of each ISAMPLE within the same subject using parallel computing threads (L2P).
The performances of the MPEM were assessed in the UK HPC cluster with 256 basic compute nodes with each node contained dual Intel E5-2670 2.6 GHz 8-core processors. Runtimes of the MEPM with a single CPU core (M-S), L1P (M-L1), and L1P/L2P (M-L12) were recorded and compared. Runtime of the MCPEM-MAP in NONMEM 7.3 with a single CPU core (N-S) was determine and used as an external reference for comparison. A one-compartment linear PK model was used to simulate PK of 100 subjects with intensive sampling design for the analysis.

Results: We first assessed the performances using a PK data of 10 subjects because UK HPC cluster policy only allowed up to 10 compute nodes per single job. ISAMPLE of 100,000 and 100 EM iterations were used to achieve small OBJ variation at steady-state and model convergence [3]. In M-L1, the **μ** and **B** of 10 subjects was computed separately in 10 compute nodes (10 L1P) and this represented the maximum parallel gain of the L1P task. In M-L12, ISAMPLE within the same subject assigned to each compute node was further distributed to 16 processor cores (16 L2P) within the compute node for μ and B computation. The runtimes were 41.8, 8.6, 1.28 and 0.800 min for N-S, M-S, M-L1 and M-L12 respectively. M-L12 computed 38% faster than the M-L1.
We then expanded the analysis to include the PK data with 100 subjects in exploring the performances of MPEM with various L1P/L2P combinations. The runtimes were 418 and 87.7 min for N-S and M-S, respectively. The runtimes were 58.3, 29.2 and 12.1 min for M-L1 with numbers of L1P task of 2, 4, and 10, respectively. The runtimes were 34.9, 17.3, and 6.97 min for M-L12 with L1P/L2P combinations of 2/16,

4/16, and 10/16, respectively. The M-L12 consistently performed faster than the M-L1 regardless of the numbers of L1P task. Similar results were observed for ISAMPLE=50,000.

Conclusions: The implementation of extra parallelization level L2P is able to overcome the computational bottleneck of L1P in accelerating the performance of parametric EM in PQP analysis. To our best knowledge, MPEM is the **first** reported parametric EM method with dual levels of parallelization in population data analysis. Study is ongoing to assess the performance of this novel MPEM in complex PQP analysis with large system of ODEs and complicated dataset. In addition, further parallelization with GPUs is being implemented to optimize the L2P process which is expected to further

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III-46: *Wenjun Chen* Modeling the antitumor efficacy and pharmacokinetic/pharmacodynamic interaction between docetaxel and cabozantinib in human prostate cancer xenograft mouse models

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Objectives: Achieving better antitumor efficacy by drug combination is a mainstay in oncology. However, the combination efficacy of antitumor drugs might not be a simple synergy. Docetaxel (Doc) is a semi-synthetic taxane microtubule inhibitor, and docetaxel plus prednisone has been the standard first-line chemotherapy in patients with castration-resistant prostate cancer (CRPC) [1]. Cabozantinib (Cab) is an orally bioavailable multi-target tyrosine kinase inhibitor [2] which has been investigated in multiple solid tumors including prostate cancer. The purpose of this study were (1) to develop a semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model to describe plasma concentration and the antitumor activity of Doc and Cab, (2) to quantitatively describe and compare the combination effect of Doc and Cab under concurrent therapy and interval therapy, with or without PK interaction considered, and (3) to investigate different sequential therapies in mouse xenograft model of CRPC.

Methods: Pharmacokinetics of Doc and Cab when administered separately and simultaneously were investigated in nude mice, and the plasma concentrations were determined using HPLC-MS/MS. The pharmacodynamic studies of Doc and Cab under monotherapy, concurrent therapy (Doc and Cab were administered simultaneously) and interval therapy (Cab was administered six hours after Doc) were performed in prostate cancer cell PC3 and 22Rv1 tumor-bearing mice, and the antitumor activity of the two drugs under different sequential therapies were investigated in PC3 xenograft model. Based on the experimental data, a semi-mechanistic PK/PD model was developed and evaluated to explore the relationship between plasma concentration and drug effect quantitatively. The proposed PK/PD model was performed using the First Order Conditional Estimation with Interaction (FOCEI) method with NONMEM and validated via VPC.

Results: The concentration-time curve of Doc was fitted by a two-compartment model, while that of Cab was described by a one-compartment model with first-order absorption. The PK interaction between Doc and Cab was expressed by adding the effect of Cab on the clearance of Doc in PK model. Gompertz and logistic model were used as the base model for tumor natural growth dynamics of PC3 and 22Rv1 xenografts, respectively. It was assumed that Doc exhibited direct cell-killing effect while Cab exerted inhibitory effect on tumor carrying capacity (the maximum sustainable tumor volume) instead of damaging tumor cells [3]. The PD interaction between the two drugs was quantitatively characterized through combination index ϕ. Our experimental results showed that the concurrent administration of Doc and Cab proved better tumor inhibition efficacy than monotherapy in both xenograft models, and the interval therapy did not enhance the anti-tumor efficacy compared with the concurrent therapy. When the PK interaction was ignored, Doc and Cab showed weak synergy in antitumor efficacy with parameter ϕ greater than one under both concurrent and interval treatment schedules. However, parameter ϕ estimated were adjacent to one after introducing PK interaction into the model, indicating that there was no significant PD synergism or antagonism between the two drugs. Tumor growth inhibition exhibited different patterns in different sequential schedules. The Doc followed by Cab (Doc ~ Cab) sequential therapy was superior to monotherapy while the Cab followed by Doc (Cab ~ Doc) sequential schedule was less effective. The effect

of the two drugs in “Doc ~ Cab” and “Cab ~ Doc” sequential schedule was synergistic and antagonistic respectively since ϕ estimated were greater than or less than one respectively.

Conclusions: The proposed PK/PD model properly described the plasma concentration and anti-tumor effects of Doc and Cab under different treatment schedules. There was no significant PD interaction between Doc and Cab in both concurrent schedule and interval schedule, while the effect of the two drugs in “Doc ~ Cab” and “Cab ~ Doc” sequential schedule was synergistic and antagonistic, respectively. The enhanced antitumor efficacy of the concurrent and interval regimen could be explained by PK interaction of the two drugs partly.

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III-47: *Mohammed Cherkaoui Rbati* A Liver Model for Chemoprotection Against Malaria

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Introduction: Malaria is a deadly threat and to prevent its spread, it is important to protect people from infection, particularly from *P. falciparum*, probably the most prevalent and and deadly human malaria strain in Africa. Chemoprotective drugs are developed for this purpose. These should be taken at regular intervals for as long as a person is at risk. The intervals should be infrequent, ideally monthly. To reach this goal, the drug must kill the parasites not only during blood-stage but also during development in the liver, the first stage of infection after an infectious mosquito bite.

Whilst PKPD models have been developed to understand and describe the blood-stage activity of potential antimalarials, hardly any model has been proposed for liver-stage activity.

In vitro [1] and preclinical *in vivo* [2, 3] experiments have been developed to assess the efficacy of drugs on the liver-stage, as well as a liver-stage controlled human malaria infection model (CHMI). However, what makes it difficult to obtain a PKPD model for liver-stage activity is that unlike for blood-stage, direct measurement of liver-stage parasites is not possible.

Objective: Develop a PKPD model to describe the drug killing effect on the liver-stage parasites. The example of DSM265, a plasmodial dihydroorotate dehydrogenase (DHODH) inhibitor, is chosen to illustrate the approach.

Methods: Two liver-stage CHMIs were conducted, where healthy volunteers were treated with a DSM265 dose of 400mg administered 1, 3 or 7 days prior to infecting them with an *i.v.* injection of 3200. A placebo group, infected but not receiving the drug, was included in each study. Exposure of DSM265 and blood-stage parasitemia were measured in all participants [4]. Since liver-stage parasitemia could not be monitored, the information on liver-stage must be deconvoluted from the knowledge of the blood-stage activity.

A mathematical model was developed which consisted of two ordinary differential equations which described respectively the dynamic of liver-stage and blood-stage parasites over time. Each equation included a net growth rate and a drug killing rate specific to each stage. One term accounted for the release of the parasites from liver-stage to blood-stage. The parameters describing the parasite dynamics were determined from the literature [5, 6]. The drug killing rates were assumed to depend on DSM265 blood concentration according to a Hill function response. The Hill coefficient was assumed to be the same for both stages; the other parameters, E_{max} and EC_{50}, were specific to the liver- and blood-stage. The blood-stage parameters were fixed to the values from a previous PKPD analysis of an induced blood-stage CHMI study. Left to be estimated: were the initial fraction of the inoculated parasites that successfully invaded hepatocytes and the liver-stage E_{max} ($E_{max,L}$) and EC_{50} ($EC_{50,L}$).

The parameter estimation was conducted with Monolix (v4.3.3), an NLME modelling software. Given the limited number of subjects, some of the inter-individual variability parameters were fixed, namely those of $E_{max,L}$, $EC_{50,L}$ and the invader fraction F_{inv} to 0, 0.3 and 0.5, respectively. For the validation of the model, multiple simulations of the CHMI studies were conducted and the predicted fraction of subjects with recrudescence was compared with the observations.

Results: Two estimations were performed; (i) estimation of $E_{max,L}$, and (ii) fixing $E_{max,L}$ to blood-stage E_{max} ($E_{max,B}$). In the first estimation, a correlation between $E_{max,L}$, $EC_{50,L}$ is observed. As the maximum effect in the liver could not be observed, the estimation did not converge. In the second estimation, as $E_{max,L}$ was fixed, the estimation converged. In both scenario, F_{inv} was estimated at 0.2% corresponding to 6 sporozoites invading hepatocytes. In comparison, it was estimated that about 35% of the 15-120 sporozoites injected after a mosquito bite invaded hepatocytes [7]. Finally, simulations showed that the final PD model could reproduce the CHMI studies' results, despite the limited number of volunteers.

Conclusion: In conclusion, combining knowledge of parasite dynamics, blood-stage and liver-stage CHMI studies made it possible to develop a PKPD model describing the activity of an antimalarial drug on both liver and blood stages. This will help select the appropriate dosing regimen for chemoprotection.

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III-48: *Manoranjenni Chetty* Antidepressants, anxiolytics and statins: prediction of exposure changes due to aging

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Objectives: Antidepressants, anxiolytics and statins are commonly prescribed in elderly patients. This group of patients are generally not included in clinical trials that investigate the relevant doses of these drugs. Drug dose regimens used in the older patients are frequently determined by trial and error or extrapolated from doses relevant to young adults. Physiological changes that may potentially impact drug exposure in the elderly are frequently reported, although they may be challenging to quantify. Physiologically based pharmacokinetic (PBPK) modelling offers the opportunity to explore and predict such changes in large virtual patient populations. The Simcyp population-based PBPK Geriatrics model accounts for age-related physiological changes such as demographic distribution, intestinal transit time, liver volume, kidney weight, renal function and some metabolic enzymes. This model does not account for frailty. The objective of this study was to predict potential differences in drug exposure between elderly and young patients, using the geriatrics and healthy volunteer models within the Simcyp simulator.

Methods: Two drugs from each of the above drug classes were selected from the Simcyp library for this analysis. They included fluoxetine, desipramine, midazolam, triazolam, pravastatin and rosuvastatin. Using the compound files within the simulator, simulations were run using 10 trials of 100 subjects each, where 500 of the subjects were young healthy Caucasians aged between 18 and 46 years, while the other 500 subjects were geriatric Caucasians aged between 66 and 80 years. Drug exposures, as assessed by area under the plasma concentration versus time curve (AUC0-t) and maximum plasma concentration (Cmax) or clearance (CL) of 40 mg fluoxetine, 50 mg desipramine, 0.03mg/kg midazolam, 0.25 mg triazolam, 20 mg pravastatin and 40 mg rosuvastatin were simulated and compared with observed values. The ratio of the predicted and observed drug exposure in both young and elderly subjects were first evaluated to verify the performance of the PBPK models. Drug exposures in elderly subjects were then compared with that in young subjects.

Results: Comparison of the predicted drug exposure in both young and elderly with the corresponding observed values indicated that the PBPK models performed acceptably for the six drugs. Predicted versus observed ratios for the comparative % decrease in exposure between young and elderly for the drugs were: desipramine 1.20; fluoxetine 1.3; midazolam 0.96; triazolam 1.26; rosuvastatin 0.75 and pravastatin 0.93. Apart from fluoxetine, where no significant change was predicted between the young and elderly, increased exposure to the other drugs was predicted in elderly subjects.

Conclusions: Acceptable predictions of the changes in the exposure of the selected drugs in elderly subjects were obtained in this study, suggesting that this approach could be a useful tool for dosage predictions in elderly subjects. Further verification of the model with a larger number of compounds is warranted.

III-49: *S. Y. Amy Cheung* Challenges and opportunities in the development of medical therapies for paediatric populations and the role of extrapolation

IQ consortium – CPLG Pediatric Working Group: S. Y. Amy Cheung1, Ashley Strougo2, Sebastian Haertter3, Jing Liu4, Steven J. Kovacs5, Solange Corriol-Rohou6, Christina Bucci-Rechtweg7, Jeffrey S. Barrett8, Raafat Bishai9, Angela James10, Dennis Potempa2 an

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Objectives: Children deserve medical therapies that have been properly evaluated for safety and efficacy and formulated specifically to meet their needs. With the release of paediatric regulations in the European Union (EU) and the United States (US), there are new opportunities for strategies that can provide robust evidence for use of medicinal products in children [1, 2]. Use of innovative approaches such as extrapolation from a reference population is now being applied to paediatric drug development – expediting articulation of dose rationales and/or replacing RCTs in children. The IQ consortium - CPLG Pediatrics Working Group's objective is to improve drug development in children by sharing knowledge amongst industry and regulators regarding their experiences related to paediatric product development process.

Methods: We reviewed and evaluated the challenges and opportunities in paediatric drug development and the role of extrapolation [3] in 4 parts, including (1) the current regulatory framework for the use of extrapolation in paediatric drug development; (2) recent discussions for potential enhancements to this regulatory framework; (3) a quantitative toolbox (i.e., model-based/informed drug discovery and development (MID3) [4] with a focus on tools and methods to support extrapolation) to advance efficiency and science in the development of new medical therapies for paediatric populations; and (4) examples of diseases/indications where extrapolation has been used and accepted by regulators are presented to identify gaps and opportunities for improvement.

Results: Part 1 provides background on paediatric regulatory policies and how modelling and simulation and extrapolation were incorporated in the recently published ICH-E11 (R1) and EMA Paediatric Extrapolation Reflection Paper. Part 2 identifies current gaps and proposes points to consider for future regulatory policy. This includes the need for disease-specific regulatory guidelines, context-specific considerations of the source data available for extrapolation, limitations of partial extrapolation, knowledge gaps and special provisions regarding therapies targeting the special needs of neonates and extrapolation for safety. Part 3 details how the application of MID3 can benefit the paediatric extrapolation framework (e.g. assumption setting/evaluation and assessment of disease similarity between adults and children). Recommendations on the use of various types of modelling including systems pharmacology modelling, empirical modelling and meta-analysis and the value and importance of read-world evidence (RWE) are also addressed. Part 4 provides case studies covering 5 disease areas (partial-onset seizures, pain, gastroesophageal reflux disease, type 2 diabetes mellitus and cancer) with application of extrapolation for 3 situations with a focus on prior knowledge, assumptions, extrapolation rationale and impact: 1) Similar disease and similar exposure-responses (ER) relationship 2) Similar disease by diagnostic criteria and different ER relationship 3) Different disease and ER relationship to compare the strength and limitation.

Conclusions: There is growing experience with quantitative approaches and data to guide the appropriate use of extrapolation in the development of new therapies for paediatric populations. However, better alignment of regulatory authorities on the definition of extrapolation and agreement on acceptable uses is still warranted. The successful application of extrapolation for paediatric patients with partial-onset seizures highlights the importance of quantitative approaches and knowledge-sharing/collaboration among stakeholders (sponsors, investigators, and regulators) to reach a mutual understanding about similarities in pathophysiology and responses to therapy. Educating others about what paediatric extrapolation and quantitative approaches are may inspire more trust, improve care, and promote collaborations or partnerships to improve the way the needs of paediatric patients are addressed in the future.

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III-50: *Maxwell Tawanda Chirehwa* Correlates of tuberculosis treatment outcomes: application of regression trees and pharmacodynamic modelling techniques

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Objectives: The long duration of therapy remains a challenge for the successful treatment of tuberculosis (TB). The study aimed to characterise the impact of pharmacokinetics of 1st-line antituberculosis drugs, and TB and HIV disease markers on TB treatment outcomes (time-to-stable culture conversion (TSCC), relapse, and death).

Methods: TB treatment outcomes were available for 150 patients who participated in the PK sub-study of the RAFA randomised clinical trial (PACTR201105000291300). The RAFA study was a three-arm trial, and patients were randomised to receive (a) efavirenz-based ART at 2 weeks after the start of standard TB treatment, (b) standard TB treatment or (c) 50% higher dose of rifampicin. Steady-state individual AUC0-24 and Cmax were derived from population PK models for rifampicin, isoniazid, pyrazinamide, and ethambutol. Sputum was collected bi-weekly in the first 8 weeks of treatment and monthly thereafter for TB culture. TSCC was defined as the time of the first observed culture negative result which was confirmed at a follow-up visit after 2 or 4 weeks. Long-term treatment outcome was defined as either treatment relapse or death in the 24 months of follow-up. Binary classification and regression trees (CART) and time-to-event (TTE) modelling were used in combination to explore this dataset. CART with conditional inference using permutation tests was applied to identify the most promising covariates effects that are predictive of treatment outcomes and interactions between these covariates (1, 2). The conditional inference methodology eliminates the bias toward selection of continuous predictors associated with ordinary CART. The result of CART analysis is a tree-like structure with binary splits and the root node represents the most significant predictor of the outcome. Additional significant covariates are added as daughter nodes in order of importance using a predefined type 1 error (α = 5%). The identified nonlinear associations in the TSCC analysis were further evaluated using TTE pharmacodynamic modelling with interval censoring. The analyses were implemented in R and Monolix 2016R1 software (3, 4).

Results: TSCC was associated with chest X-ray grading, WHO HIV stage before TB diagnosis, and study arm. TTE-CART identified X-ray grading as the most important covariate associated with TSCC: patients with at most advanced X-ray grade were separated from patients with very advanced X-ray grade (median TSCC = 22 vs 29 days respectively, p value= 0.004). Among patients with very advanced X-ray grade, patients classified as HIV stage 2 before TB diagnosis had faster TSCC compared to those in stage 3 or 4 (median TSCC = 21 vs 29 days respectively, p value= 0.048). In the last step, patients with advanced HIV disease, initiating ART at 2 weeks was associated with faster TSCC compared to standard treatment or high dose rifampicin (median TSCC = 28 vs 36 days respectively, p value= 0.043). Further analysis using TTE pharmacodynamic modelling showed that patient with very advanced X-ray grading, advanced HIV stage, and who did not start ART at 2 weeks converted later than the rest of the cohort (median TSCC: 36 vs 23 days, p value<0.001). Death or relapse was observed in 20/150 patients in the cohort. Patients with lung cavitation were more likely to either relapse or die (25% vs 11%, p value= 0.045). Among patients without lung cavitation, being not physically active (i.e. confined to bed) was associated with relapse or death (24% vs 6, p value= 0.021). The CD4+ count was associated with treatment outcome in patients who did not

present with lung cavitation and were physically active. A higher proportion of poor treatment outcome was observed in patients who had lower (< 100 cells/microL) CD4+ count (17% vs. 2%, p-value=0.006)

Conclusions: We combined time-to-event regression trees and pharmacodynamic modelling techniques to describe the relationship between tuberculosis treatment outcome vs drug exposure, disease burden, and patient characteristics. Drug exposure was not found to be associated with either TSCC or long-term TB treatment outcomes, contrary to previous reports (5). Treatment outcomes were correlated with tuberculosis and HIV related disease severity markers. The identified markers could be used to profile patients with high or low risk of treatment failure and to tailor a treatment strategy based on the patient profile.

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III-51: *Jason Chittenden* PMDatR: A Pharmacometric Data Manipulation Package for R

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Objectives: The creation of NONMEM or similar datasets often involves interactions between multiple groups: a vendor that creates the raw datasets; the pharmacometrician that specifies the desired content and format of the analysis data set; data programmers who construct the dataset according to specifications; and quality control personnel who verify the dataset contents. Tools that preserve the rigor of the traditional approach while reducing the cycle time and enabling pharmacometricians to take greater ownership of the final dataset can increase the efficiency of the overall modeling and simulation workflow.

Methods: PMDatR builds on top of popular R packages such as dplyr[1] and tidyr[2], so much of the syntax is well known and documented. The key features that facilitate data work flows include: functions for transforming, reformatting (such as automatically unstacking covariate columns in result domains like LB), and verifying inputs; common transformations such as filling forward; computation of ADDL dosing; unit aware columns and transformations; and automated code generation from a settings file. Some common transformations include: automatic conversion of date/time formats; change from baseline; time after dose and similar calculations; and filling of missing covariate values. The settings file, provided in YAML format, allows for integration with customized graphical user interfaces. In addition, the settings file can be used to provide sensible and standardized default settings.

The overall process for dataset construction follows: 1) load source data and convert to standardized formats using customizable mappings; 2) assign source data sets to a 'type' of data (observation, dose, merged covariates, event covariates) and apply mappings and transformations; 3) stack event type data and merge covariates by key columns; 4) apply transformations and filters that require the entire dataset (e.g. time after dose).

Results: PMDatR is already in use in-house where it enables standardization of scripting style and quality control efforts. It is also in use at a major pharmaceutical company where it underpins a dataset creation tool having a graphical user interface to provide settings to the PMDatR package and collect and display results. The approach that links PMDatR as a back-end to a graphical user interface allows for additional features such as: drag-and-drop selection of columns and transformations; point-and-click selection of options and templates; syntax and semantic error checking; and additional help features for less experienced R programmers.

Conclusion: PMDatR provides a framework for pharmacometric dataset creation that is useful both as a standalone R package that provides a few additional tools for data manipulation, and as a powerful backend to more feature rich graphical user interface base applications that can integrate it into a data management ecosystem. In both cases, the benefits of a reusable, templatized, workflow can result in faster dataset creation and improved dataset quality.

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III-52: *Young-Kyung Choi* Population pharmacokinetics of cycloserine in patients with multidrug-resistant tuberculosis

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Objectives: Cycloserine is a bacteriostatic anti-tuberculosis drug used in combination for the treatment of multidrug-resistant tuberculosis (MDR-TB). Cycloserine remains a 'second-line' TB drug because of its frequent CNS effects. Symptoms range from headache and somnolence to severe psychosis, seizures, and suicidal ideas. Serious CNS toxicity may be associated with elevated serum or plasma concentrations, because there is no appreciable barrier to CNS entry for cycloserine. And low plasma concentrations may lead to therapeutic failure and development of drug resistance due to incomplete eradication of Mycobacterium tuberculosis. Therefore, it is important to clarify dosing conditions that may impair or promote achievement of adequate cycloserine plasma concentrations. However, the pharmacokinetics (PK) of cycloserine has not been studied in Korean patients. The objectives of this study was to describe the population PK of cycloserine in Korean patients with MDR-TB and to identify significant covariates affecting its disposition.

Methods: Serial blood samples were collected from the patients and population PK analysis was performed using nonlinear mixed effects modeling (NONMEM, version 7.3: Icon, Inc., Ellicott City, MD, USA). Population was undertaken using the first-order conditional estimation (FOCE) method with interaction. Sex, age, weight, comorbidities, and creatinine clearance (calculated by Modification of Diet in Renal Disease formula) were investigated as potential covariates on the PK parameters.

Results: Twenty-five Korean patients with MDR-TB aged 20 to 78 years included in this study. The mean body weight and creatinine clearance were 56.6 kg (range, 46-73) and 87.6 mL/min/1.73m^2 (range, 41.7-118.3), respectively. A one-compartment model with first-order absorption and elimination described PK of cycloserine. The estimated total body clearance and volume of distribution were 0.84 L/hr and 22.8 L, respectively. Clearance was decreased according to creatinine clearance which was explained using power model. We were not able to characterize fully the creatinine clearance in our model, and this was mostly due to the lack of sufficient patients who have low or/and high CL_{CR}. Cycloserine does not bind to plasma proteins and approximately 70% of dose is excreted by the kidney, unaltered, within 72 hours. Besides, base model incorporating CL_{CR} on CL/F was not only reduced the AIC level but also improved visual inspections of goodness-of-fit plots. Furthermore, when the model included the effect of CL_{CR} on CL/F, objective function value is slightly decreased from the simple exponential error model (△OFV=3.412). For these reasons, it is reasonable to base model including CL_{CR} on CL/F. Other covariates from demographic and clinical information did not significantly further explain the PKs of cycloserine.

Conclusions: The PK behaviors of cycloserine were well described by the developed population PK model. This model can be helpful to set therapeutic drug monitoring system for anti-TB drugs including cycloserine. Additional studies will be needed to further validate the suggested results.

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III-53: *Francois Combes* Modeling and Simulation Approach of Everolimus PK/PD Toward Completing a Pediatric Development

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Objectives

Epilepsy is a common feature in patients with tuberous sclerosis complex (TSC), occurring in up to 85% of patients; approximately 60% of these patients remain treatment-refractory. Everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, is approved in Europe as an adjunctive therapy for patients aged ≥2 years with TSC-associated treatment-refractory partial-onset seizures, based largely on results from the EXIST studies, notably EXIST-3 study (NCT01713946). Analyses were performed to assess everolimus exposure and efficacy: For exposure, a physiologically based pharmacokinetic (PBPK) model was built and qualified based on pharmacokinetic (PK) data from pooled studies, in which the youngest observed patient would have started everolimus at approximately age about 1 year. For efficacy, the EXIST-3 study, where the youngest patient started everolimus at the age of 2 years, was the only study performed in this indication. Consequently, all built models are qualified for patients aged ≥1 year for PK and ≥2 years for pharmacodynamic (PD). As TSC-associated seizures can also affect children between 6 months and 2 years, a modeling and simulation (M&S) approach was taken to predict the expected exposure and corresponding efficacy (short-term via population PD [3], and long-term via linear mixed effect models) of everolimus as adjunctive treatment in patients aged between 6 months and 2 years with TSC-associated treatment-refractory seizures. The aim of this approach was to understand whether the recommended dose of 6 mg/m^2 would bring patients aged between 6 months and 2 years old to the everolimus target range of 5-15 ng/mL, resulting in a reduction from baseline in seizure frequency (RSF).

Methods

The M&S study consisted of a framework of 3 models that were used together to enable the prediction of reliable patient exposure metrics (trough concentrations, C_{min}) in children between 6 months and <1 year, and efficacy metric (RSF) in children between 6 months and 2 years. A PBPK model using SimCYP® simulation software was developed to predict C_{min} over a 2 year period in pediatric patients initiating everolimus at an age between 6 months and 2 years. A total of 200 patients (replication of 10 trials with 20 patients each) were simulated. A population PD (PopPD) model and a linear mixed effect model were used to predict respectively short-term (after 6 months of treatment) and long-term (after 24 months of treatment) efficacy in terms of RSF, using the PBPK-predicted daily C_{min} values.

Results

The PBPK model predicted that the simulated C_{min} at the end of 24 weeks QD treatment for simulated patients of ages between 6 months and 2 years was in the range of 7.7-10.5 ng/mL, well within the targeted range of 5-15 ng/mL used in older patients. Predicted concentrations in younger patients who started everolimus before the age of 2 years were slightly higher than those observed in older children and adults included in EXIST-3. Using this predicted C_{min}, the PopPD model predicted that the RSF would be of at least 66.1% (5th-95th percentiles: 50.3-75.8%) for a patient starting everolimus at the age 2 years and 77.8% (5th-95th percentiles: 60.6-87.6%) for a patient who started everolimus at an age of 6 months. Similar results were found when using the linear mixed effect model which used time-normalized predicted

C_{min} computed over 12-week intervals as the exposure covariate. Based on the long-term model-based analysis, the RSF observed in EXIST-3 was 21.39% (95% confidence interval [CI]: 13.30-28.74) for a 2-fold increase in time-normalized C_{min}. Every additional 12 weeks of exposure to everolimus was predicted to have a modest, but significant effect on SF, resulting in a further decrease of SF by 5.64% (95%CI: 3.54-7.70) per period. Additionally, a 0.5-fold lower baseline SF was predicted to reduce RSF by 49.41% (95%CI: 45.68-52.89). The parameter estimates from this model and the time-normalized PBPK predicted C_{min} were used to predict long-term efficacy. On an average, about a 50% RSF was predicted at the first 12 week time point and a reduction of around 70% at the final time point (2 years).

Conclusion

Based on the results of the M&S study, everolimus at the dose of 6 mg/m^2 is anticipated lead to an efficacious treatment in children aged 6 months to 2 years, with concentrations within the recommended target range.

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III-54: *Valerie Cosson* Population PKPD modeling of RO7046015 (PRX002/RG7935), an Anti-α-Synuclein Monoclonal Antibody for the treatment of Parkinson's Disease

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Objectives: RO7046015 (also known as PRX002 or RG7935), a monoclonal antibody (Ab) targeting alpha-synuclein (aSyn), is currently in development for the treatment of Parkinson's disease (PD). The objectives of the analysis are to describe the PK of RO7046015 and the PKPD relationship between free RO7046015 serum concentrations and free and total aSyn serum concentrations in healthy subjects during the Single Ascending Dose (SAD) study and PD patients during the Multiple Ascending Dose (MAD) study using population approach.

Methods: RO7046015 and aSyn samples were collected in two phase 1 double-blind, placebo-controlled studies: a SAD in healthy subjects and a MAD (3 doses administered 4 weeks apart) study in PD patients. Healthy subjects were enrolled into 5 ascending-dose cohorts and randomly assigned to receive an intravenous RO7046015 dose of 0.3, 1.0, 3.0, 10, 30 mg/kg or placebo. PD patients were enrolled into 6 ascending-dose cohorts and randomly assigned to receive an intravenous RO7046015 dose of 0.3, 1.0, 3.0, 10, 30, 60 mg/kg or placebo. In total, data from 40 healthy subjects and from 80 PD patients were included in this analysis. A sequential approach [1, 2] was followed: RO7046015 serum concentrations were fitted first to a pharmacokinetic model and subsequently the relationship between free, total aSyn and RO7046015 serum concentrations were fitted to a full target-Ab binding model [3]. All models were developed using non-linear mixed-effects modelling implemented in NONMEM V7.2.0 [4]. Simulations using the PK model were performed to compare the distribution of exposure metrics between weight-based dosing and flat dosing.

Results: The PK of RO7046015 was adequately described by a 3-compartment mammillary disposition model with first-order elimination. Good precision of the fixed and BSV on CL and V1 were obtained with RSE below 25%. The PK of RO7046015 was similar in healthy subjects and PD patients. The estimated clearance was equal to 0.583 L/day, approximately 2.5-3 fold higher than predicted for a typical IgG1 [5]. The population effective half-life equals ~14 days. As for many therapeutic monoclonal antibodies, body weight was found to have a significant effect on the PK of RO7046015, with both clearances and volumes function increasing with weight with a power of 0.837 for clearances and of 0.625 for volumes. When compared with the value of CL in a patient weighing 76 kg, the CL decreased by 34% for patients with the lowest weight (i.e., 46 kg) and increased by 32% for those with the highest weight (i.e., 106 kg). Similarly, weight positively correlated with V1, leading to a deviation from typical of −29% for patients with the lowest weight and +26% for those with the highest weight. The simulations showed that the distributions of the exposure metrics largely overlap between the weight-based and flat dosing.

The PKPD relationship between free RO7046015 and both free and total aSyn serum levels was adequately described with a full target-antibody binding model. Reasonably good precision of the fixed and random effect parameters were obtained: the RSE were between 5 and 38% except for BSV on complex elimination for which the RSE was 61%. The estimated in vivo KD is found similar in healthy subjects (75 nM) and in patients (90nM). The comparison of the simulated PKPD profiles of free and total aSyn shows a quasi-complete overlap between the two populations. The steady state for decrease of free aSyn and increase of

total aSyn is achieved after 5 monthly IV administrations of RO7046015. At steady-state, RO7046015 maintains the free aSyn serum concentrations below 22, 48 and 67 % of the baseline over the dosing interval of 10, 30 and 60 mg/kg dose, respectively.

Conclusions: As RO7046015 is always in excess compared to free aSyn in serum even at low doses, the target-mediated elimination pathway of RO7046015 is saturated and its PK is linear over the dose range. The PK of RO7046015 supports the use of flat dosing. A trend for higher exposure in patients with lower weight can be mitigated by selecting a lower dose for these patients. The PKPD model confirms a clear dose-dependent binding of free RO7046015 to free aSyn in serum.

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III-55: *Perrine Courlet* Comparison of escitalopram pharmacokinetics in HIV infected individuals with an uninfected psychiatric cohort

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Objectives:

The rate of depression in patients with HIV is higher than in the general population with up to 40–60 % of HIV-positive subjects reporting depressive symptoms (1-3). Citalopram and escitalopram (S-citalopram), its marketed pharmacologically active enantiomer, are among the most prescribed antidepressants in HIV-infected and uninfected psychiatric patients. Both R- and S-citalopram enantiomers are metabolized equally by the cytochrome P450 isoenzymes (CYP): CYP2C19 (≈37%), CYP3A4 (≈35%), and CYP2D6 (≈28%) (4). The aim of this observational study was to compare the pharmacokinetic profile of escitalopram in HIV-infected individuals with uninfected psychiatric patients, to identify sources of variability that could influence drug exposure, and notably to evaluate drug-drug interactions (DDI) with antiretroviral treatments. Indeed, citalopram and escitalopram are among the antidepressants with the highest risk of QT prolongation, and escitalopram overexposure due to DDI could yield to an increased risk of QT prolongation and arrhythmias (5).

Methods:

Fifty-two plasma samples at unselected time after the last citalopram (n=27) or escitalopram (n=25) intake were collected from 39 HIV-infected patients in the framework of a Swiss HIV Cohort Study (SHCS #815). To estimate escitalopram dose and plasma concentrations from the racemate (citalopram), the total doses were divided by two and plasma concentrations were derived using an S/R ratio of 0.45 (6). Moreover, 115 uninfected psychiatric patients receiving escitalopram provided 212 plasma samples during an ongoing pharmacogenetic study (PsyMetab). Escitalopram pharmacokinetics were analyzed using the non-linear mixed effect modeling (NONMEM®) program. The effect of subject specific continuous (age) and discrete covariates (cohort, citalopram treatment, sex, and co-medications) was explored. Antiretroviral treatments were classified as known CYP2C19 inducers (28% of the HIV-infected patients), CYP3A4 inducers (5%) or inhibitors (44%), as well as p-glycoprotein inducers (10%) or inhibitors (36%).

Results:

A median of one sample (range 1–2 for HIV-infected patients and 1-11 for uninfected psychiatric patients) of citalopram or escitalopram was collected per patient. The pharmacokinetic profile was similar in patients receiving citalopram and escitalopram, supporting the S/R ratio in plasma of 0.45. A one-compartment model with first order absorption and elimination best described escitalopram pharmacokinetics. Due to the paucity of data during the absorption phase, the absorption rate constant was fixed to 0.8 h^{-1} according to the literature (7, 8). Average escitalopram clearance (CL/F) was 25.7 L/h (RSE 7%), and volume of distribution (V/F) 1410 L (RSE 34%). An inter-subject variability was assigned only on CL/F and was estimated to 54%. None of the tested covariates had an impact on CL/F. Despite the broad range in the participants age (18 - 87 years old), age was not associated with a decrease in CL/F, as opposed to

previously published data (9, 10). Of interest, antiretroviral drugs including HIV protease inhibitors did not affect escitalopram concentrations probably due to the contribution of multiple cytochromes in its metabolism and elimination, thus limiting the impact of drug-drug interactions. This observation is consistent with the lack of effect of ketoconazole, another strong CYP3A4 inhibitor, on citalopram pharmacokinetics (11).

Conclusions:

Escitalopram pharmacokinetics did not differ between HIV patients treated with antiretroviral and uninfected psychiatric patients. Although the limited amount of data limits the study power to find out small-sized effects and would require further analysis, this work presents reassuring results concerning the risk of drug-drug interaction between escitalopram and antiretroviral treatments.

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III-56: *Vincent Croixmarie* Use of a multivariate distribution to simulate severe renal impaired patients

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Objectives: Specific studies with renal impaired (RI) patients are usually carried out for drug exposure assessment in this special population. Patient recruitment for this class of patients is difficult, especially for severe RI patients. In this exercise a model based approach was used to simulate such patients. Available data for an anti-cancer drug in normal, mild and moderate RI patients were used to simulate severe RI patients, and an available population PK model was used to simulate the corresponding exposure of these patients. The simulated exposures were then compared to the observed data.

Methods: The covariates included in the population PK model were simulated using a multivariate normal distribution (body surface area (BSA), CRCL and serum albuminuria (ALB)). Additional relevant demographic covariates were also simulated (age and gender), in order to include also these covariates in the correlation. Continuous and categorical covariates were simulated as previously described [1], but in this case the covariate simulation was also extrapolated outside of the range of the available covariate values. The empirical distribution available was used to define a continuous multivariate normal distribution (MVND) which was used to simulate the virtual patients. Ranges of the real covariates were then used as boundaries to filter realistic sets of covariates with the exception of Creatinine Clearance (CrCl) with the objective to extend the simulation range to severe patients. For CrCl, the upper limit was set to the value of the real population, while for the lower limit, it was set to the lower limit for severe RI patients (15 ml/min/1.73m^2). The available population PK model was then used to simulate the exposure of these patients. The exposures of virtual patients were then compared with the real exposure of real patients. For the severe RI patients, only 4 patients were available.

Results: The exposures of normal, mild and moderate RI “simulated” patients are in agreement with the exposures obtained in available previous studies. The exposures of severe RI “simulated” patients were compared with the limited data available (4 patients) and their exposure was in agreement with these measurements. These simulations provided as additional information an estimation of the expected variability in exposure, confirming that the dose adjustment suggested for the severe RI patients should be maintained. The covariate simulation also unveiled a relationship between BSA and renal impairment which was present in the available data but which was not in agreement with the observed severe patient data. Additional investigation will be conducted in order to clarify the origin of such correlation, which can generate a bias in the simulation.

Conclusions: In this work, a distribution based method was used to simulate virtual patients for which data were not available and difficult to obtain. A prediction in this fragile population was then possible confirming the proposed dose adjustment. Particular attention needs to be addressed when covariate correlations are used to extrapolate covariate relationship outside the observed range, since this may generate bias in the simulation.

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III-57: *Ailing Cui* Quantitative Predictive Models for the Degree of Disability After Acute Ischemic Stroke

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Objectives: Stroke is one of the most common causes of disability worldwide. The levels of disability and handicap among the survivors may vary [1]. Of clinical and imaging variables, ischemic lesion volume measured on brain imaging is an objective surrogate of stroke severity and burden, which is analogous to tumor size in cancer patients. As the ischemic lesions dynamically change over time during the acute phase of stroke, it is believed that the assessment of ischemic lesion growth at multiple times may be a more reliable predictor than lesion volume at a single time. It has been demonstrated that ischemic lesion growth is an independent predictor of poor outcome in stroke patients with any stroke subtype as well as in patients who have received thrombolysis [2–6]. We sought to identify the predictive factors for the degree of disability 3 months after stroke [7] and to evaluate the quantitative predictive ability of each identified predictor for the prognosis using modeling and simulation analysis.

Methods: Prospectively collected clinical data from 405 patients with acute ischemic stroke including brain magnetic resonance images (MRIs) and disability outcomes assessed using the modified Rankin Scale (mRS) 3 month after the onset of disease were analyzed and the potential covariates were then tested with regard to whether they improved the model significantly [8]. A proportional odds cumulative logit model was implemented in NONMEM. The relationship between the difference in lesion volume (DLV) — lesion volume measured by brain MRI 5 days later — lesion volume at the onset of the disease, and the mRS measured at 3 months (mRS3) was modeled first, and the potential covariates were tested. For internal validation of the pharmacodynamic models by comparing the observed proportion of each mRS3 value and the model-predicted value by DLV, simulation with 1000 replicates was performed using the original data set, and the results are visualized in bar plots based on prespecified intervals of DLV using R software.

Results: Inclusion of TDLV in the baseline proportional odds cumulative logit model in the form of a simple maximum effect (Emax) model best described the relationship between TDLV and the logit probability of mRS3, and improved the model fit significantly compared with baseline model without TDLV. In the final mod el, TDLV, NIHSS, age, and the comorbidity of DM were identified as significant covariates.

Conclusions: The quantitative model constructed in the current analysis will enable us to predict the long-term disabilities of the patients with acute ischemic stroke using the patient-specific MRI and other clinical information. Our study findings will be useful for individualizing therapies and these results could also be applied to stratify or enrich clinical trials by predicting the prognosis of patients, thus enabling more efficient clinical drug development for patients with ischemic stroke.

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III-59: *André Dallmann* Characterization of paracetamol hepatotoxicity during pregnancy through physiologically-based pharmacokinetic modeling

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Introduction: Paracetamol (acetaminophen) is one of the most commonly prescribed drugs for acute pain during pregnancy [1]. Despite its frequent use during pregnancy, little is known about the risk of hepatotoxicity in both pregnant women and their fetuses. The aim of this study was to develop and evaluate a physiologically-based pharmacokinetic (PBPK) model that predicts the disposition of intravenously administered paracetamol and its metabolites in term pregnant women. The model was then scaled to the late first trimester and maternal disposition of paracetamol and its metabolites was predicted with the aim to characterize the hepatotoxicity risk.

Methods: PBPK models for paracetamol and its metabolites generated by uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1, sulfotransferase (SULT) 1A1, and cytochrome P450 (CYP) 2E1 were built using the Open Systems Pharmacology software suite together with the therein implemented compound templates (www.open-systems-pharmacology.org) [2]. Owing to missing information, detoxification of the CYP2E1-metabolite (NAPQI) by glutathione conjugation could not be modeled. It was therefore assumed that the concentration of paracetamol cysteine conjugates (APAP-cys) is equivalent to NAPQI concentration. Once qualified for a reference population of adult women, the model was scaled to pregnancy according to a previously described workflow [3] using a system-specific model parameterization for pregnancy [4-6]. Since quantitative information on pregnancy-induced changes in UGT1A1 tissue concentrations was lacking, the model was informed by a herein presented in vitro-in vivo intersystem extrapolation approach. Based on reported animal or human data, SULT1A1 tissue concentrations were assumed to be unaffected by pregnancy [7,8] and CYP2E1 tissue concentrations were assumed to be constantly increased by 80% in pregnancy [9,10]. The disposition of paracetamol was predicted in a population of term pregnant women and evaluated using in vivo data [10]. After successful model qualification, it was scaled to the late first trimester and maternal disposition of paracetamol and its metabolites was predicted. The risk for hepatotoxicity was then assessed through the predicted exposure to APAP-cys in the late first trimester and at term pregnancy.

Results: The simulated disposition of paracetamol in populations of non-pregnant women was in good agreement with observed in vivo data. All simulated paracetamol plasma concentrations were within a 2-fold error range. As judged from observed metabolite urine concentrations, the disposition of paracetamol metabolites was also well described by the model. The pregnancy PBPK model predicted paracetamol disposition in term pregnant women reasonably well. All predicted paracetamol plasma concentrations were within a 2-fold error range. Based on the extrapolation approach for UGT1A1 expression, the activity at term pregnancy was estimated to be on average 6-fold higher compared to non-pregnant women. Urine concentrations of paracetamol metabolites were adequately predicted, although those of paracetamol glucuronide were slightly overestimated. Scaling of the model to the late first trimester of pregnancy showed that the exposure to APAP-cys was approximately 30% higher compared to term pregnancy.

Conclusions: The developed pregnancy PBPK model accounts for physiological changes during pregnancy, such as altered organ weights, blood flows and enzyme activity. UGT1A1 activity at term pregnancy was adequately estimated by the presented extrapolation approach. This approach should be further evaluated using in vivo data of additional UGT-substrates at different stages of pregnancy. Importantly, the model can be scaled to earlier gestational weeks allowing an investigation of paracetamol hepatotoxicity throughout pregnancy in silico. While the underlying assumptions of the model, such as pregnancy-induced changes in CYP2E1 activity or concentration equivalence of NAPQI and APAP-cys, should be tested by further research, the presented results show that maternal exposure to APAP-cys was higher in the first vs. third trimester. This suggests that the risk of hepatotoxicity is higher in early pregnant women stressing the importance of careful dose selection. Ultimately, the clinical usefulness of this model could be further enhanced by investigating and predicting placental transfer of paracetamol and fetal exposure to paracetamol and its metabolites.

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III-60: *Kaschek Daniel* An Integrated R-Based Framework for Model Development in Health Economics

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Introduction: Health economic decisions rely on the evaluation of complex systems. The complexity demonstrates itself in several aspects: (1) each patient might be affected by a series of different events that render possible future consequences more or less probable, (2) the target population for a therapy may be quite different from the overall population and, (3) several alternative therapies might be available that have specific advantages and disadvantages, both in terms of cost and utility. It is the complexity and multitude of possibilities that makes modelling and simulation an indispensable tool for decision making in health economics.

To date, several independent software tools have been used to generate such models. However, models cannot be easily exchanged and exported into a readable, self-explanatory representation. Thus, proving the validity of a model to decision-makers constitutes a major difficulty.

Objectives: To develop a software framework for health economic modelling with a focus on Discretely Integrated Conditions and Events (DICE) models [1] and Markov models [2]. The major features of the core framework are model set-up by a newly developed R-based modelling language, simulation and analysis as well as interoperability with existing modelling tools via a standardized interchange format. The overall goal of the new modelling language is to render model formulation more concise and, therefore, easier to understand for external persons.

Methods: The DICE approach is a recently developed formalism to set up health-economic models for single patients or cohorts of patients. Models consist of “conditions”, describing all relevant aspects of a patient’s state, and “events”, causing sudden changes of conditions and triggering consequent events. In Markov models, events correspond to transitions which occur in every time step. Conditions in DICE models can be mapped to Markov states. However, depending on the multitude of independent patient conditions, the number of representative Markov states can excessively increase due to the combinatorial explosion. The DICE concept covers Markov models as a special case. It is, therefore, especially suited to building the core of a general modelling framework that would allow to set up, simulate and analyze a variety of health-economic models.

Results: Based on a selection of published Markov and DICE models [3, 4], we have developed a concept core modelling framework acting on three different levels. The central level is an R based Health Economic Modelling (RHEM) language by which both, DICE and Markov models can be represented. The RHEM language is designed to be expressive and concise allowing the formulation of models in few lines of humanly readable code with inline model documentation.

Underneath the RHEM language, we have implemented a simulation engine that uses the DICE algorithm to simulate DICE and Markov models. Markov models are internally converted to fit the DICE specification. Various utility functions have been implemented to visualize simulation and analysis results obtained from the simulation of our RHEM models.

To connect to already existing platforms like heRo3 [5] or EviDICE [6], we have developed a standardized JSON-based exchange format called RHEMJ that enabled us to import the published models from those platforms. The RHEMJ specification allows for model-related content like conditions, events, states, transitions to be stored. In addition, data, analysis and simulation results can be accommodated in RHEMJ.

Conclusion: Health-economic modelling has a major impact on the estimated value of a drug. By the conception of an R based Health Economic Modelling framework we set out to simultaneously establish a standard interchange format and a reference implementation to import or set up those models and simulate them. The new RHEM modelling language employed within the framework maximizes readability and intuitive understanding of complex models creating trust in the validity of the model.

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III-61: *Kim Dao* Evaluation of exposure to vancomycin in neonates under existing dosing regimens using a population pharmacokinetic approach

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Objectives:

Several neonatal pharmacokinetic (PK) models of vancomycin and dosing algorithms have been elaborated in the last three decades. (1) Among 20 different dosing approaches, retrieved from international guidelines, protocols used in neonatal intensive care units (NICUs) in Switzerland and published models, most use age, renal function and body weight as covariates to establish the appropriate starting dosage. An absence of consensus regarding which dosing regimen is best suited for neonates is nevertheless being observed, probably in relation with the absence of well-defined therapeutic intervals. Our objectives were first to build a population PK model of vancomycin in a large cohort of neonates and secondly, to compare by simulation vancomycin exposures under existing dosage recommendations with the aim of harmonizing vancomycin dosing in neonates admitted in NICUs in Switzerland.

Methods:

Based on a large neonatal therapeutic drug monitoring population, 1848 vancomycin concentrations from 405 neonates were included in the analysis. A one-compartment model with first-order elimination was developed while testing the influence of age (gestational age (GA), postnatal age (PNA), postmenstrual age (PMA=GA+PNA)), current body weight (WT) and renal function (creatinine (CRT)) related covariates known to influence vancomycin blood levels in neonates (NONMEM®). Vancomycin concentration-time profiles resulting from the 20 identified dosing regimens were predicted applying the final model developed in our population. The exposure target was defined as the ratio of the area under the curve from 0 to 24 h (AUC_{0-24}) over the minimal inhibiting concentration (MIC) after the first dose ≥ 400 based on the recommended target for Methicillin Resistant Staphylococcus Aureus (MRSA) of ≤1 mg/L (2), to the potentially toxic AUC_{0-24} of ≥ 700 mg·h/L (3). Exposure to vancomycin was evaluated after 1 day of treatment to assess early exposure. AUC_{0-24} was derived by numerical integration in NONMEM©. Exposures to vancomycin were then expressed as the proportion of patients in the target of AUC_{0-24}/MIC between 400 and AUC_{0-24} < 700 mg·h/L.

Results:

A one-compartment model adequately described vancomycin concentrations. WT using an allometric scaling was straightaway included on all PK parameters. An interpatient variability was assigned on clearance (CL), but no interindividual variability could be estimated on the volume of distribution. Among all tested covariates, PMA using a sigmoid E_{max} maturation function and CRT had the most salient impact on vancomycin CL. The significant covariates explained altogether 43% of interpatient variability in CL. An increase of CRT from 52 to 114 µmol/L (for a neonate of 1.2 kg and a PMA of 32 weeks) will reduce CL by 46%. A decrease of PMA from 32 to 28 weeks will reduce CL by 48%, whereas an increase in PMA from 32 to 36 weeks will increase CL by 27%. In the final model, the average CL was 0.268 L/h (CV 22.5%) for a WT of 1.2 kg, a PMA of 32 weeks and a CRT 52 µmol/L and the average volume of distribution was 0.629 L.

Out of the 20 evaluated regimens, the median proportion of neonates predicted within and over the target was 39% (range 4 – 77%) and 1% (range 0 – 68%), respectively. Three of these regimens, Neonatal Formulary 7 (4), Neofax® (5) and the dosing algorithm published by Janssen E *et al* (6) were associated with the highest proportion of target attainment after 24h of treatment, in 66%, 67% and 77% of patients; the proportion of patients over target was 2%, 2% and 15%, respectively. The first two international guidelines propose simple dose stratifications based on seven different categories of PMA and/or postnatal age (PNA), whereas the very detailed dosing algorithm from Janssen *et al* includes 19 levels based on PNA and body weight following a loading dose. The simple dosing regimen issued from the summary of product characteristics for vancomycin (*i.e.* a loading dose of 15 mg/kg, a maintenance dose of 20 mg/kg, every 12 hours for a PNA < 7 days and every 8 hours for a PNA > 7 days) ranks close to them with 65% of patients in target (and none over).

Conclusions:

These results suggest that simpler but also more elaborated vancomycin dosing regimens do only allow the attainment of an optimal $AUC_{0\text{-}24h}$/MIC ≥ 400 and a $AUC_{0\text{-}24}$ < 700 mg·h/L in 65 - 77 % of patients. It remains to determine if a better algorithm can be designed to optimize early vancomycin treatment in neonates without increasing toxicity, while favoring parsimony.

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III-62: *Olivier David* A PKPD model describing the amyloid precursor protein (APP) derived peptides in subjects receiving CNP520, a BACE-1 inhibitor.

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Objectives:

One important pathological feature of Alzheimer disease (AD) is the presence of deposits forming amyloid plaques in the brain cortex of affected individuals. These plaques are constituted of aggregated fibrils of Aβ peptides [1] thought to be involved in the pathophysiology of AD [2]. The amyloid cascade hypothesis [3] states that deposition of Aβ is a very early event in the pathogenesis of AD, and will ultimately lead to neurodegeneration and dementia of the Alzheimer type. Strategies that target decreasing the Aβ generated from amyloid precursor protein (APP) are potential therapeutics. APP is known to be cleaved by the α-secretase to form the sAPP-α protein and by the β-secretase (BACE-1) forming sAPPβ and C99 (other processes are likely involved). The latter is further cleaved to form the Aβ peptides.

CNP520 is an orally-available, centrally active and potent inhibitor of BACE-1. CNP520 by reducing Aβ generation and restoring Aβ equilibrium offers the promise of disease modification in AD.

The goal of this population pharmacokinetic/pharmacodynamic (PK/PD) analysis was to characterize simultaneously the dose-exposure and the exposure-response (cerebro-spinal fluid (CSF) concentrations of Aβ-40, sAPPα and sAPPβ peptides) of CNP520.

Methods:

The popPK/PD modeling was performed on clinical data from a first-in-human, single and multiple ascending oral dose study in healthy adult and elderly subjects (n>200).

The plasma CNP520 and CSF concentrations of the Aβ-40, sAPPα and sAPPβ peptides were fitted simultaneously to a PK/PD model using non-linear mixed-effects modelling implemented in Monolix 2016R1. Data preparation and graphical outputs were generated using R 3.2.3 (library ggplot2).

Results:

CNP520 PK was best described with a linear two-compartment model with an absorption lag time, sequential zero- and first-order absorption processes and first-order elimination. Plasma concentrations of CNP520 were well described and parameters estimated precisely.

The rate of production of APP was assumed to be constant and coded as a zero-order process. The elimination of APP was assumed to occur via the α-secretase or the BACE-1 only. The formation and the elimination of Aβ-40, sAPPα and sAPPβ peptides were assumed to be first-order processes.

The drug effect was modeled by linking plasma CNP520 concentrations to CSF Aβ-40 and sAPPβ concentrations via an indirect response population PK/PD model (Imax model with a Hill coefficient), in which CNP520 inhibited the sAPPβ and Aβ-40 synthesis and by indirect effect increased the production of

sAPPα. This model estimated a maximal CSF sAPPβ and Aβ-40 inhibition (Imax) of more than 95% with a concentration associated with 50% of the maximum effect (IC50) of approximately 20 ng/mL. The model described adequately the concentrations of Aβ-40, sAPPα and sAPPβ peptides in CSF following CNP520 administration. The model parameters were estimated with a good precision (relative standard error less than 10% for most of them).

Conclusions: The plasma PK of CNP520 and its PD effects on three CSF peptides were modeled simultaneously. The model described the data adequately and can be used for further work, such as dose selection and recovery time to baseline values.

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III-63: *Nico de Jager* Population pharmacokinetic modelling of factor VIII levels during perioperative dosing of Haemate® P (Humate P) in patients diagnosed with von Willebrands Disease.

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Objectives: Von Willebrand factor/factor VIII (VWF/FVIII) concentrate Haemate® P (Humate P) is widely used in treatment of patients diagnosed with Von Willebrand’s Disease (VWD). These patients are characterised by a qualitative or quantitative defect of VWF. VWF is essential in primary and secondary hemostasis as it mediates adhesion and aggregation of platelets at sites of vascular injury, and acts as a chaperone protein for FVIII by protecting it from premature clearance. Treatment consists of replacement therapy using clotting factor concentrates in cases of acute or perioperative bleedings aiming to correct the VWF (and FVIII when present) deficiency. The objective of this study is the development of population pharmacokinetic (PK) algorithms for the perioperative situation, which could allow more accurate dosing of clotting factors, reducing consumption without increasing the bleeding risk.

Methods: VWD patients undergoing minor or major surgery in the Academic Medical Centre Amsterdam, Erasmus Medical Centre, Leiden University Medical Centre, Radboud University Medical Centre or University Medical Centre Groningen between 2000-2015 who received Humate® P were included in the dataset for this study. The retrospective data, consisting of FVIII levels, were analysed using nonlinear mixed-effects modelling (NONMEM v7.4) in combination with the First-Order Conditional Estimation with Interaction (FOCE+I) method. [1] With respect to endogenous FVIII baseline levels, historical baseline measurements were added to each observation in order to produce more accurate individual predictions. As pre-operative FVIII levels were occasionally higher then FVIII baseline levels, a ‘virtual’ dose was introduced in the data. A bioavailability parameter is used in each occasion to correct for this difference, without affecting the PK estimates. Covariate relationships, containing demographics, surgery characteristics and clinical features, were evaluated using a forward inclusion- followed by a backwards elimination method to explain inter-individual variability (IIV). A bootstrap method was used to check the robustness of the PK parameter estimates. Model performance evaluations were based on goodness-of-fit plots and visual predictive checks (VPC).

Results: PK parameter estimates were based on 96 adult and 8 pediatric VWD patients, undergoing 139 and 8 surgeries respectively. Median age, body weight and surgery duration (range) were 51 years (0.5-82), 77 kg (8.8-118) and 81 minutes (7-470), respectively. Furthermore, median FVIII baseline values and pre-operative FVIII levels (range) were 0.41 (0.01-0.97) and 0.76 (0.01-3.11) IU, respectively. The included patients were diagnosed with type I (n=55), type IIA (n=24), type IIB (n=7), type IIM (n=9), type IIN (n=3) or type III (n=6) VWD. PK profiles, containing 734 FVIII level observations were best described using a one-compartment model. A proportional error model was used to describe residual variability. PK parameters were allometrically scales using the ¾ power-model for Vd an CL. Typical values of the model for the volume of distribution (Vd) and clearance (CL) were 4.6 L/70 kg and 0.032 L/h/70 kg, respectively. Corresponding inter-individual variability of Vd and CL were 34% and 69%. The residual error was 0.23%. Covariate analysis identified an association between CL and the duration of the surgery: CL decreases as surgery duration increases. Furthermore, patients in ASA class III or IV exhibited a 41% decrease of CL.

Bootstrap results confirmed the robustness of the model. Furthermore, the VPC of the final model, using 1000 replicate simulations of 104 patients, resulted in predictions of the simulated data that were well-matched with the observed level-time profiles.

Conclusions: Time-courses of obtained perioperative FVIII levels after administration of Humate® P were described adequately by the developed PK model. This model facilitates PK-guided dosing of Humate® P in VWD patients undergoing a minor or major surgical procedure, which potentially likely result in improvement of quality and cost-effectiveness of care.

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III-64: *Giuseppe De Nicolao* Analysis of muscular biopsy distributional data in Duchenne Muscular Dystrophy treatment: a population approach

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Objectives: Limited treatment options are currently available for Duchenne Muscular Dystrophy (DMD), the most common muscular dystrophy in childhood [1]. To objectively assess the efficacy of possible new treatments, muscle fibers cross sectional areas (CSAs) can be measured via skeletal muscle biopsies, at baseline and at least once after treatment. Being biopsy a destructive procedure, the measured tissue specimen changes on each occasion. As pre- and post-treatment fiber CSAs cannot be paired, their empirical distributions in the two occasions are compared. Here, it is shown how distributional data can be analysed within a population approach framework. In particular, the histological effects of the HDAC1 inhibitor Givinostat are assessed, based on data collected in a DMD clinical trial [2].

Methods: In the phase II DMD clinical study (sponsored by Italfarmaco S.p.A; study identifier: NCT01761292), 20 boys aged from 7 to For each patient, pre- and post-treatment CSA empirical distributions are compared in order to assess Givinostat-induced changes from baseline. A hierarchical statistical approach is proposed to identify CSA distributions and estimate drug effect on CSA, both (i) for each patient (lower level of the hierarchy) and (ii) in the population (higher level).
Lower level.
For the single patient, each fiber is seen as a sample drawn from a population of fibers. The pre- and post-treatment distributions of log-transformed CSAs (logCSAs) are modelled as two-component Gaussian mixtures. Drug effect on logCSAs is described by a shift, corresponding to a multiplicative factor on CSAs, intended as a drug potency parameter. Mixtures and shift are estimated in NONMEM 7.3 (FOCE). Muscle composition data are used for model validation: post-treatment tissue fractions (muscle fiber/fibrotic/fat/necrotic) are model-derived and compared to observed ones.
Higher level.
Typical values for the patient population and inter-patient variabilities are computed via Global Two Stage (GTS) and their uncertainty evaluated via boostrap.

Results:
Lower level.
The model describes well the distributional data. For all patients the drug potency parameter is >1 (shift>0) i.e. the CSAs increase following Givinostat treatment. All parameters are reliably estimated (CV%<~30% for all patients). The model-derived post-treatment muscle composition values are comparable to the observed ones.
Higher level.
Due to dose reductions in study Part 2, computation of typical parameters and inter-patient variabilities via GTS was performed separately on Group A (dose=25 mg BID) and Group B (37.5 mg BID). Drug effect was found to be stronger in Group B (drug potency parameter=2.05, vs 1.57 in Group A). Typical mixture parameters are comparable between the two groups. Inter-patient variability (CV%) in Group B is at most around 30%, while in Group A it exceeds 50% for some parameters. According to bootstrap, the uncertainty in typical values estimates has maximum CV%~5% for both groups. Uncertainty in inter-patient variabilities

is comparable between Group A and B (CV%~20%), except for two terms, whose uncertainty is higher in Group B (CV%>80%).

Conclusions: The analysis of muscular distributional data has been addressed via a hierarchical statistical approach that has been applied to assess Givinostat therapeutic effects on DMD patients. Both the distribution of fiber CSA and the drug potency (summarized by a multiplicative factor on fiber sizes) have been characterized. At the lower level, pre- and post-treatment logCSA distributions were described via two-component Gaussian mixtures, identical apart from a shift. Drug potency was estimated as >1 for all subjects, indicating that Givinostat has positive histological effects; for Group B (higher dose), drug potency was stronger with respect to Group A. The predictive performance of the model was confirmed by muscle composition data. The validity of this novel modeling framework may extend to several other contexts (other diseases/drugs/measures) where outcomes are obtained as distributional data.

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III-65: *Mailys De Sousa Mendes* Mechanistic modelling of in-vitro bidirectional permeability studies and in vivo absorption of metoprolol

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Objectives: Bidirectional transport assays can be used to obtain *in vitro* permeability estimates for use in PBPK models. However, the conventional analysis of these assays makes several assumptions that can impact the quality of the *in-vivo* prediction. For example, it assumes that sink conditions are maintained, which can be difficult to achieve experimentally, especially for highly permeable compounds. It also assumes that the unstirred water layer (UWL) doesn't have significant impact on the observed permeability and the impact of compound ionisation is not usually studied. We to developed a model that mechanistically describes the *in-vitro* permeability across Caco-2 cells for metoprolol, a highly permeable drug. The impacts of ionisation and UWL on the permeability were investigated.

Methods:

In-vitro assay:

Data for the bidirectional transport of metoprolol across Caco-2 monolayers were previously generated [1]. Briefly, Caco-2 cells were seeded at a density of 1x 10^5 cells/well onto 12-ellTranswell® inserts and grown for 23 ±1 days prior to permeability experiments. Experiments were performed at 37°C, with apical and basolateral volumes of 0.5 and 1.5mL, respectively, and was stirred at 450 rpm (calibrated plate shaker (BMG LabTechnologies GmbH, Offenburg, Germany). The basolateral compartment was buffered to a pH of 7.;, whereas a range of buffer pH values was investigate in the apical compartment (pH 5.0, 5.5, 6.0, 6.5, 7, 7.4, 7.7 and 8.0)

Data analysis (modelling):

A mechanistic model was developed in R software (version 3.3.1) and included 5 compartments, representing apical and basolateral bulk media and unstirred water layers in addition to the cell monolayer. The fraction ionised was calculated in each compartment and for each experiment based on the drug pKa and media pH values. The total unstirred water layer thickness was predicted on the basis of stirring rate using data from Adson *et al.* [2]. The permeability of the ionised form (was calculated using the permeability of the neutral form and an ionisation scalar describing the log decrease in permeability for cationic metoprolol compared to the neutral species.

Simulations:

The permeability estimates obtained were implemented in the metoprolol compound file in the Simcyp Simulator v17. The Mechanistic passive regional permeability predictor (MechPeff) model was used to predict the effective permeability observed in human ($P_{eff,man}$). This $P_{eff,man}$ was used to predict the absorption using a first-order model and the Advanced Dissolution, Absorption and Metabolism (ADAM) model. Plasma concentration-time profiles of metoprolol after a single oral dose of 100 mg in CYP2D6 extensive metabolisers were simulated for 10 trials of 16 female subjects 18 – 40 years and compared to observed data from Sharma *et al.* [3].

Results:

The *in vitro* model was able to describe the decrease in metoprolol permeability with an increase in ionisation. The difference between the observed and predicted *in-vitro* concentrations was less 2-fold. The geometric mean fold error (GMFE) was 1.27 and the geometric fold bias (GMFB) was 1.02. The $P_{trans,0}$ estimate of 40000 10^{-6} cm/s and ionisation scalar of 3.4 predicted an $P_{eff,man}$ in the jejunum I of 2.95 10^{-4} cm/s when applied in the metoprolol PBPK model. The mean (± SD) clinically observed *in-vivo* C_{max}, t_{max} and AUCwere 0.89 ± 0.42 µmol/l, 1.69 ± 0.63 h and 4.05 ± 2.15 µmol.h/l respectively. With a first-order absorption model the mean (clinical range) predicted C_{max}, t_{max} and AUC were 0.75 (0.64-0.85) µmol/l, 1.59 (1.48-1.66) h, 4.26 (3.37, 5.16) µmol.h/l, repectively. With the ADAM model the mean (clinical range) predicted C_{max}, t_{max} and AUC were 0.62 (0.53-0.71) µmol/l, 2.21 (2.01-2.33) h, 4.18 (3.32, 5) µmol.h/l, repectively.

Conclusions:

The mechanistic model was able to account for the impact of metoprolol ionisation on its passive permeability *in vitro*. When *in vitro* permeability estimates were applied in the metoprolol PBPK model, the predicted *in-vivo* absorption was in accordance with clinical data, indicating that this approach could be used to generate robust inputs for PBPK models.

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III-66: *Elien De Thaye* In vitro data supporting circulating CCCK18 as potential pharmacodynamic biomarker in ovarian cancer

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Objectives: Circulating full-length and caspase-cleaved (cc) cytokeratin (CK) 18 are used in the study of apoptosis and chemotherapy-induced cell death. In patients with epithelial tumors, cytokeratins hold potential as biomarkers due to their epithelial specificity, abundance and cleavage by caspases. An in vitro cell-based assay was performed to investigate the potential of these two pharmacodynamic biomarkers in view of their use in personalized cancer treatment.

Methods: NIH:OVCAR-3, SK-OV-3, SK-OV-3LucIP1, PA-1 and Caov-3 ovarian cancer cells were exposed to increasing concentrations of paclitaxel (0 to 1000 nM) during 24 hours. Following exposure of all cell lines, levels of cleaved and intact CK18 were assessed in the culture medium, up to 5 days after washing away treatment, by specific ELISA assays (M30 Apoptosense® and M65 EpiDeath® ELISA, VLV*bio*, Sweden). In addition, cell survival was investigated using a MTS assay (CellTiter 96® AQ_{ueous} One Solution Cell Proliferation Assay, Promega, The Netherlands). 72 hours after washing away the treatment solutions, cell survival and ccCK18 release data were analysed using, respectively, a full inhibitory and stimulatory sigmoidal E_{max} model with NONMEM® (version 7.3.0, ICON, Hanover, MD, USA).

Results: In all cell lines, the 1 to 1000 nM paclitaxel concentrations were effective in inhibiting cell proliferation. The cumulative amount of released ccCK18 increased with increasing paclitaxel concentrations for all cell lines. The concentration-effect relationships for both cell survival and ccCK18 levels showed similar trends in terms of paclitaxel concentration needed to reach 50% of its effect (C50). Exposure-response modeling of the paclitaxel effects regarding cell survival resulted in estimated C50 values equal to 26.4 nM (SK-OV-3LucIP1; 23% RSE (relative standard error), 95% CI: 14.503 – 38.297), 10.4 nM (SK-OV-3; 31.3% RSE, 95% CI: 4.01 – 16.79), 9.06 nM (PA-1; 0.1% RSE, 95% CI: 9.039 - 9.081), 8.49 nM (NIH:OVCAR-3; 0.4% RSE, 95% CI: 8.425 – 8.555) and 1.91 nM (Caov-3; 15.2% RSE, 95% CI: 1.34 – 2.48). C50 parameters from the exposure-response modeling of the drug effects focusing on the released amount of ccCK18 were estimated to be 8.05 nM (SK-OV-3LucIP1; 5.4% RSE, 95% CI: 7.199 – 8.901), 6.41 nM (SK-OV-3; 17.6% RSE, 95% CI: 4.195 – 8.625), 3.66 nM (NIH:OVCAR-3; 9.9% RSE, 95% CI: 2.95 – 4.37), 1.15 nM (PA-1; 0.5% RSE, 95% CI: 1.139 – 1.161) and 0.834 nM (Caov-3; 1.2% RSE, 95% CI: 0.814 – 0.854). Regarding the cell survival data, C50 values increased from Caov-3, over NIH:OVCAR-3, PA-1 and SK-OV-3 to SK-OV-3LucIP1. Regarding the ccCK18 data, the same trend was observed, except for a switch between PA-1 and NIH:OVCAR-3. No pharmacodynamic analysis was performed based on the in vitro release data for total levels of CK18 as, except for the PA-1 cell line, it was difficult to observe clear differences in released amounts over drug concentration levels.

Conclusions: Based on this in vitro study, evidence of association was demonstrated between paclitaxel-induced cell toxicity and resulting ccCK18 levels based on the similar outcome in terms of C50 values across cell lines. This in vitro work illustrates the potential for using ccCK18 levels as a surrogate for cell survival.

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III-67: *Aurelia de Vries Schultink* Therapeutic drug monitoring of endoxifen in ER-positive breast cancer patients: comparing data from clinical practice to model-based predictions.

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Objectives:

Five years of adjuvant treatment with tamoxifen lowers estrogen receptor (ER)-positive breast cancer recurrence and mortality rates. Despite tamoxifen's effectiveness, resistance to treatment occurs. Variability in response has been attributed to variability in pharmacokinetics (PK), more specifically to variability in endoxifen concentrations, an active metabolite of tamoxifen. Both endoxifen concentrations and the *CYP2D6* genotype, responsible for bio-activation of tamoxifen, have been proposed as predictive markers for recurrence. Therapeutic Drug Monitoring (TDM) of endoxifen seems the best way forward to tailor tamoxifen treatment, since variability in concentration of endoxifen can only partially be attributed to *CYP2D6* genotypes. An endoxifen concentration >5.97 ng/mL has been associated with 26% lower risk of breast cancer recurrence, in a retrospective analysis (1). This target can be applied to tailor tamoxifen treatment, recommending an increase in tamoxifen dose from 20 mg to 40 mg daily if endoxifen concentrations are below this threshold. In order to evaluate the feasibility of a prospective validation of this threshold, a PK model that represents clinical practice is needed. Models describing the PK of tamoxifen and its metabolites are sparse and based on data from trials only. However, TDM is implemented in clinics, and might have different proportions of patients reaching the target. Therefore, the aim of this analysis is to evaluate target attainment based on endoxifen TDM applied in a clinical cohort and compare to model-based predictions from a PK model based on trial data.

Methods:

Breast cancer patients treated with tamoxifen in the adjuvant setting and for whom TDM of endoxifen was applied in the Netherlands Cancer Institute, were included. Samples were drawn >3 months after start of treatment and after dose adaptation, ensuring steady state. Since PK data in this population was sparse, target attainment before and after dose adaption was compared to predicted proportions based on a previously reported 4-compartment PK model (2). We assumed an underlying CYP2D6 phenotype distribution with 52.5% extensive/ultra-rapid, 45% intermediate and 2.5% poor metabolizers, as previously described (3), other covariates were imputed as the median. Subsequently, 10,000 patients were simulated using a dose adaptation simulation script (R version 3.3.1) including inter-individual variability and residual error. Dose was adapted based on a sample at day 90 and reevaluated on day 180.

Results:

In total, 976 samples of 713 patients were available, of which 658 patients had a first sample taken during treatment of 20 mg tamoxifen daily. In this group, 203 patients (33%) did not reach the target concentration. Of these 203 patients, 120 patients received a dose increment to 30 or 40 mg depending on the measured endoxifen concentration, of which 82 patients (68.3%) reached the target at the second sample. The simulation analysis demonstrated that 32.6% of the simulated patients did not reach the TDM

target of 5.97 ng/mL. This was in accordance with the proportions in clinical practice (33%). However, after dose adaption to 40 mg of the initial patients below target, 85.1% simulated patients reached the target, compared to only 68.3% of patients who received a similar dose increment in the clinical setting. In total, after applying TDM to the clinical cohort, 73% of all patients attain the target at the second sample, compared to 88.4% in the simulated cohort. Since only a part of the patients in the clinical cohort received a dose increment, a sensitivity analysis was conducted. This analysis showed that if all patients with below-target endoxifen concentrations would have received a dose increment, 83.1% compared to 73% of all patients in the clinical cohort would reach therapeutic levels of endoxifen.

Conclusions:

This analysis demonstrated that the effect of TDM on endoxifen target attainment is over predicted by considering only trial data. Around 15% of the subjects are falsely assumed to reach the target. This is partly caused by the assumption that all below-target patients receive a dose increment, though side effects hamper this in the clinical setting. Additionally, patients included in a trial are assumed to be more adherent to therapy than patients in clinical practice. These findings should be considered when evaluating feasibility of prospective validation of TDM for endoxifen.

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III-68: *Neel Deferm* A Mechanistic Cellular Disposition Model of Bile Acid Handling in Sandwich-Cultured Human Hepatocytes

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Objectives: To develop a physiological model which describes hepatic uptake, metabolism and biliary excretion of the bile acids (BAs) chenodeoxycholic acid (CDCA) and its glycine-conjugate glycochenodeoxycholic acid (GCDCA) in sandwich-cultured human hepatocytes (SCHH) and to utilize it to quantify differences in estimated kinetic parameters between day-2 and day-6 cultures.

Methods: *In vitro* disposition data were obtained by incubating SCHH with 2.5, 10 or 25 µM CDCA. Incubation buffers containing CDCA and GCDCA were collected, followed by cell lysis to determine intracellular levels. Additionally, biliary excretion of CDCA and GCDCA were determined. An ordinary differential equation (ODE) model was fitted to concentration and amount-time profiles with NONMEM (ICON plc) Version VII level 3.0 using a proportional error model and the first-order conditional estimation with interaction (FOCE+I) method for analysis [1]. The model includes compartments representing the buffers, cells, bile and cells+bile with compound distributed among them through linear processes. Model selection was based on the log-likelihood criterion, goodness-of-fit plots, and scientific plausibility. Initial parameter estimations were obtained from simulations using Berkeley-Madonna v8.3.23.0. Culture time (day-2 or day-6) and phase (loading or efflux) were implemented as dichotomous covariates in the dataset. Statistical significance of covariate effects on kinetic parameters was assessed using a stepwise covariate method involving testing of covariate relationships in a forward inclusion (reduction of objective function value (ΔOFV) of 6.63; P<0.01) and backward exclusion (ΔOFV of 10.8; P<0.001).

Results: A mechanistic ten-compartment disposition model was developed which adequately described the *in vitro* disposition of CDCA and GCDCA. Total (passive + active) intrinsic unbound uptake and efflux clearance of CDCA were estimated to be 4 (± 6%) µL/min/10^6 cells ($CL_{int,u,up,CDCA}$) and 2 (± 1%) µL/min/10^6 cells ($CL_{int,u,eff,CDCA}$), while estimates of the total (passive + active) intrinsic unbound uptake and efflux clearance of GCDCA were 0.5 (± 1%) µL/min/10^6 cells ($CL_{int,u,up,GCDCA}$) and 0.6 (± 2%) µL/min/10^6 cells ($CL_{int,u,eff,GCDCA}$). Total (passive + active) intrinsic unbound biliary clearances of CDCA and GCDCA were estimated at 6 (± 4%) µL/min/10^6 cells ($CL_{int,u,bile,CDCA}$) and 5 (± 12%) µL/min/10^6 cells ($CL_{int,u,bile,GCDCA}$), whereas the estimate of intrinsic unbound metabolic clearance ($CL_{int,u,met}$) of CDCA was 18 (± 7%) µL/min/10^6 cells. Covariate analysis showed a statistically significant effect ($p < 0.01$) of culture time on $CL_{int,u,eff,GCDCA}$ (day-2: 0.6 (± 1%) µL/min/10^6 cells, day-6: 1.7 (± 2%) µL/min/10^6 cells) and $CL_{int,u,met}$ (day-2: 17.7 (± 3%) µL/min/10^6 cells, day-6: 7.2 (± 11%) µL/min/10^6 cells).

Conclusions: Modeling of *in vitro* BA disposition suggests that the hepatic elimination of CDCA is mostly dominated by its conversion to GCDCA, while biliary excretion clearance of unchanged CDCA represents about 28% of the metabolic clearance.

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III-69: *Oleg Demin* Simulations of tau-targeted therapies using quantitative systems pharmacology model of tau pathology

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Objectives: Accumulation of pathological forms of tau protein is one of the key hallmarks of neurodegenerative diseases. Unlike amyloid pathology, tau pathology in intracellular and thus it is even more complicated target in the context Alzheimer's disease treatment, although it probably may be more related to neurodegeneration. Long timescale of the related processes and lower clearance rate (in comparison with, ex. amyloid beta) makes clinical studies especially challenging and does not allow to obtain information from short term PD studies. Therefore, for quantitative analysis and simulations systems pharmacology modelling can be especially valuable tool. For the prediction of the results of tau targeted therapy we propose a mechanistic model describing such tauopathies as Alzheimer's disease (AD), and frontotemporal degeneration (FTD) in human and tau accumulation in preclinical tauopathy model, mice carrying P301S(L) tau mutation.

Methods: The model describes tau production, tau-microtubules interaction, tau modification, aggregation and propagation through different brain compartments. The compartments of the brain have been constructed specifically to capture Braak stages of Alzheimer's disease: 1-2 (transentorhinal), 3-4 (limbic) and 5-6 (isocortical). It was shown that the tau pathology propagation is determined by the connectivity, but not proximity [1], thence our model reproduces the key memory retrieval model components for simplification [2] which also correspond approximately to the Braak stages of AD. Thus, three regions of the brain were considered: EC (entorhinal), HP (hippocampus and limbic system), CT (neocortex). To describe multisite tau protein phosphorylation, we developed the specific approach based on the partial independence of site phosphorylation [3] and taking into account the key kinases (GSK3b, CDK5) and phosphatase PP2A. Tau oligomers serve as the key intermediates for fibril growth and as mediators of tau pathology connectivity-driven propagation from entorhinal cortex through limbic system to neocortex. The driver of longitudinal disease progression in AD model is the decrease of degradation of tau fibrils. For FTD case we use the information about tau mutation influence on polymerization and microtubule binding obtained from the in vitro data. The phosphorylation model parameters were calibrated using in vitro data on tau phosphorylation. The in vivo human model versions were calibrated across published biochemical data for soluble, insoluble tau, CSF tau and PET (^{18}F-AV-1451 SUVR) data [4]. The mouse model was calibrated across biochemical data for soluble (RAB, RIPA soluble fractions), insoluble tau (FA soluble fraction) in several brain structures, interstitial fluid and CSF of mouse.

Results: The model describes reliably consecutive appearance of PET signal in different regions corresponding to Braak stages of AD. Model verification on FTD patient data revealed that tau propagation parameters differ from AD patient. The mouse model version satisfactorily describes reduction of soluble tau and accumulation of insoluble tau in the brain of the mouse P301S(L). Tau pathology propagation and gradual appearance of polymerized tau starting from entorhinal cortex through the limbic system to neocortex is also predicted correctly and follows the experimentally observed trend. Data on immunotherapy by antibodies HJ8.5 in mouse are described satisfactorily only if significant (10 times) increase of insoluble tau degradation is assumed, while blocking the tau propagation only does not allow for description of the mouse data. Analogous degradation activation in humans would lead to complete disappearance of tau in AD patient but would cause moderate effect in FTD patient according to the model.

Conclusions: The proposed QSP model could be considered as a platform for investigation of therapeutic impact on tau pathology and translational analysis. It can be further integrated with amyloid pathology model [5] for better understanding of AD pathology.

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III-70: *Oleg Demin Jr* Quantitative Systems Pharmacology Modeling of CAR-T Therapy and T Cell Engaging Bispecific Antibodies: B-cell Acute Lymphoblastic Leukemia Case Study

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Objectives: T cell engaging bispecific antibodies (T-BsAb) and chimeric antigen receptor T cells (CAR-T) are very promising types of immunotherapy for cancer. It is established that these types of treatment work well in leukemia. Indeed, there are several therapies that have already been approved to treat patients with B-cell acute lymphoblastic leukemia (B-ALL). These therapies are CD3/CD19 bispecific T cell engager (blinatumomab) and anti-CD19 CAR-T (tisagenlecleucel). Moreover, there are a lot of other T-BsAb and CAR-T therapies for B-ALL targeting CD19, CD20 or CD22 in pipelines of pharmaceutical companies. The aims of this work are: (1) to develop quantitative systems pharmacology (QSP) model describing T-BsAb and CAR-T therapies in B-ALL; (2) to evaluate factors affecting patients' response and non-response to the treatment; (3) to prioritize the potential targets (CD19, CD20, CD22) for B-ALL treatment.

Methods: QSP model of B-ALL treatment with T-BsAb and CAR-T was developed. The model is based on ordinary differential equations (ODE). It includes description of hematopoiesis of normal B cells (including naïve B cells, CD20 negative and CD20 positive precursors of B cells), leukemic blasts, CD4 and CD8 T cells, different cytokines (IL-2, IL-6, TGF beta, TNF alpha and other) in physiological compartments (bone marrow, blood/plasma). Model describes pharmacokinetics and pharmacodynamics of blinatumomab (CD3/CD19 T-BsAb) [1] and CAR-T targeting CD19 receptor (19-28z CAR-T, 2nd generation of CAR-T including CD28 costimulation domain, developed by Memorial Sloan-Kettering Cancer Center) [2]. Model part describing normal hematopoiesis and B-ALL progression was calibrated on the basis of in vivo data on cells and cytokines level in blood and bone marrow of healthy subjects and relapsed/refractory B-ALL patients. Parameters describing blinatumomab and CAR-T were initially fitted against in vitro data on specific lysis of B-ALL cell lines, cytokines production and activation of T cells during culturing of T cells with target cells in presence of blinatumomab or culturing of CAR-T cells with target cells. Then, part of clinical data was used to re-calibrate some parameters. Other part of clinical data was used for model validation.

Results: The model is able to describe clinical data on dynamics of leukemic blasts, different subsets of T cells and cytokines during treatment of B-ALL patients with blinatumomab and CD19 CAR-T. Model successfully reproduces the clinically observed data on decrease of cytokine release if treatment starts with lower dose of blinatumomab followed by dose increase to the optimal values. It was shown that expression level of target receptor on cancer cells is very important factor affecting treatment success. In general, CD19 is better target than CD20 and CD22 due to the higher expression on leukemic cells. But due to the high inter-patient variability of CD19, CD20 and CD22 expression on leukemic blasts, different receptors could be effective as a target for treatment of particular patients. Expression of CD3 (in case of T-BsAb) and chimeric antigen receptors (in case of CAR-T) are another important factors affecting response/non-response. Model shows that proportion of CD19+ and CD19- leukemic blasts could be used as a predictive biomarker to predict probability of relapse in patients treated with therapies targeting CD19 and to stratify patients.

Conclusions: Developed model accurately captures available clinical data. Model shows the importance of CD19, CD20 and CD22 expression as a potential predictive biomarkers and key biomarkers to choose the

right target for the therapy. Model could be used as a tool for optimization of B-ALL patients' treatment with T-BsAb and CAR-T.

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III-71: *Aris Dokoumetzidis* Population pharmacokinetics of teicoplanin in preterm and term neonates with late-onset sepsis

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Objectives: Although glycopeptides are among the most commonly used antimicrobials in neonates with suspected late-onset sepsis, little is known about the pharmacokinetics (PK) of teicoplanin in term and preterm neonates. We aimed to develop a population pharmacokinetic model in order to evaluate currently recommended dosing regimen. The sparse PK clinical study was desgned prospectively by use of D-Optimal design.

Methods: By using D-Optimal design approach with the OptDes MATLAB code and literature priors from a children study [1], a sparse PK study was designed and implemented in 60 neonates with post-menstrual age (PMA) of 26-43wks. Dosing regimen: loading dose 16mg/kg, maintenance dose 8mg/kg once daily (i.v. 30min infusion). Four blood samples per neonate were collected. Concentrations were quantified by high-pressure liquid chromatography–mass spectrometry. Population PK analysis was performed using NONMEM software while covariates were tested based on clinical and statistical significance, with an allometric rationale while alternative options were also tested. Final PK model was validated by nonparametric bootstrapping and visual predictive check. Monte-Carlo (MC) simulations were carried out for various doses, to assess probability of target attainment (PTA) using 2 different targets, $C_{trough(120h)}$>15mg/L and AUC/MIC>400, the latter for a range of MIC values.

Results: D-Optimal design methodology determined 3 sampling groups of patients with 2 sampling times on each of the 1st and the 5th day, respectively, which was implemented in the hospital closely. The final model was a 2-compartment model with the following relationships for the PK parameters: clearance, CL=0.0227*(WT/1765)^0.75*(CRCL/22)^0.672 L/h, central volume, V1= 0.283*(WT/1765) L, intercompartmental clearance, Q=0.151*(WT/1765)^0.75 L/h and peripheral volume, V2= 0.541*(WT/1765) L. Inter-individual variability on clearance (CL), central volume (V1) and peripheral volume (V2) was 37%, 46%, 51.4%, respectively. For the MC simulations a model without the CRCL on CL was used which has similar parameter estimates, in order to avoid assumptions on the distribution of CRCL. Simulations demonstrated that with a dose of 8 mg/kg: 81.6% of neonates with weight (WT)<1kg versus 89.6%, 95.1% and 97% of neonates with WT 1-2kgr, 2-3kg, ≥4kg, respectively, reach the target of $C_{trough(120h)}$>15mg/L. Increase in dose at 11mg/kg results in 91.9% of neonates with WT<1kg achieving $C_{trough(120h)}$>15mg/L. Also using as a target AUC/MIC>400 the smaller WT band needed a higher dose of 11 mg/kg to achieve 90% at MIC=1 mc/ml, 1- 2 kg band achieved 93% with 10 mg/kg while higher WT bands achieved 89.7% and 92.7% PTA with 8 mg/kg, respectively.

Conclusions: We present a very informative PopPK model for pre-term and term neonates with late onset sepsis, utilizing a well implemented D-optimal design sampling scheme. The results indicate that teicoplanin PK is variable in neonates, with body WT having the most significant impact on the parameters, while CRCL is also an important covariate on clearance. Based on MC simulations ELBW and VLBW neonates below 2 kg may need higher doses than the 8 mg/kg currently recommended in the SPC, especially for *Staphylococcus* spp. with MIC≥1 mc/ml, while for neonates of WT>2 kg, the recommended doses seem to be adequate.

According to these findings, there seems to be no need for TDM contrary to what was suggested recently by other authors [2].

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III-72: *Artem Dolgun* A functional, integrative R environment workflow for the development and use of quantitative systems pharmacology models

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Objectives: Quantitative systems pharmacology (QSP) is becoming an established modeling methodology used in drug development [1]. QSP modeling has found successful applications at different stages of pharmaceutical R&D [2]. Key factors limiting further expansion of QSP expansion are: (1) methodological issues, *e.g*., as related to complexities of parameter uncertainty estimations and model identifiability issues originating from typically sparse experimental data and often originating from multiple sources; (2) a lack of unified modeling tools, which would enable an analysis through a consistent modeling workflow, from data inputting to model development and simulations to reporting. We thus developed an integrated workflow intended to enable QSP type analyses, with industrialization features to allow for the processing of various data types (at both study and subject levels) and to provide programming support with broad analytical functionality [3]. In this work, we feature a solution for the industrialized development of mechanistic and semi-mechanistic systems pharmacology models, for both individual- and study-level data, in an R environment.

Methods: The workflow was implemented in R software (Version 4.3) and is further based on the IQR systems pharmacology and pharmacometrics toolbox (version 0.6.1) developed by IntiQuan [4], as well as the AZR tool (version 0.0.0.9) developed by AstraZeneca [5]. Graphical user interface for the workflow was developed in R shiny (version 1.0.5). IQR's parameter estimation method [6] was used for the estimation of parameters using study-level data. This estimation method is based on a maximum-likelihood estimator, using a trust-region optimizer. The gradient and the Hessian are determined with high numerical precision through the use of symbolically derived parameter sensitivity equations. Confidence intervals for the estimated parameters are determined via the Fisher Information Matrix. In addition, IQR enables the calculation of point-wise finite sample confidence intervals through likelihood profiling, using the algorithm published in [7]. Estimation of parameters based on individual-level data was performed through NONMEM or Monolix fitting algorithms.

Results: The workflow for the development of mechanistic QSP models was established in a highly flexible syntax, using available IQR and AZR tools. The workflow enables the following steps: compilation of a standardized dataset; data exploration; parameter estimation procedures; model diagnostics; sensitivity/identifiability analyses; assessment of uncertainty around predicted mean; and generation of a report. A standardized '.csv' dataset is used as input to the abovementioned packages, with a unified structure for the different data types; this allows for calling of population software, through the R environment, for individual-level data and manual handling without programming software, if study-level data were to be used for parameter estimation. Once the dataset is compiled, it is ready for automated processing, to the last phase of the workflow.
Goodness-of-fit metrics and a rich toolkit for model testing, e.g., Observed vs. Predicted and Residual plots as well as longitudinal profiles are incorporated into the main framework routine.
Sensitivity analysis is implemented in the workflow using a host of curves and tornado plots for selected timepoints. Identifiability of estimated parameters is assessed by measuring the gradient and the Hessian for the objective function, and objective function profiling.

Monte-Carlo simulations were applied to generate multiple trial data by simulating experimental data from mean and SE and, therefore, to obtain estimation of parameter distributions taken into observed uncertainty in the data.
Automated generation of a QSP modeling report is the last step of the established workflow. The workflow is compliant with RSTAN, which supports the development of fully Bayesian QSP models based on the Hamiltonian MC methods.

Conclusion: In this work, we propose an industrialized workflow for the development of mechanistic and semi-mechanistic systems pharmacology models, applicable at both study- and individual-level data, using R-based packages, and further integrated with commonly used software in Pharmaceuticals, such as NONMEM and Monolix. Such a functional, integrative workflow enables all key steps, from data inputting to report generation, necessary to perform and apply QSP modeling.

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III-73: *Anne-Gaelle Dosne* Optimizing Biomarker-Based Dosing Algorithm for Erdafitinib through PK-PD Modeling and Simulations

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Objectives:

To guide a phosphate-based dosing algorithm for erdafitinib, an orally administered panfibroblast growth factor (FGFR) tyrosine kinase inhibitor, using PKPD modeling and simulation.

Methods:

An integrated PKPD model linking the time course of plasma concentrations of erdafitinib to serum phosphate levels, an on-target PD marker of FGFR engagement, was built using data collected in 373 subjects enrolled in six Phase 1 and Phase 2 studies. Subjects included were healthy volunteers and advanced cancer subjects, including subjects with metastatic or unresectable urothelial cancers with FGFR genomic alterations. Erdafitinib was orally administered either as a solution, capsules, or tablets (reference formulation). Doses investigated were single and continuous once daily (QD) doses from 0.5 to 12 mg or intermittent (7 days on/7 days off) dosing regimens of 10 and 12 mg QD. In the patient studies, dose modifications and dose interruptions were performed according to study guidelines based on phosphate levels and other toxicity biomarkers. Due to high protein binding (>99.5%), both free and total concentrations were measured. Parameter estimation was performed with NONMEM (7.3.0), dose optimisation and evaluation of the dosing algorithm rules was assessed though PKPD model based-simulation with Simulo (6.4.1). Diagnostics were obtained via R (3.2.3).

Results:

A semi-mechanistic PK model, including the interaction with alpha-1-acid glycoprotein (AGP), to which erdafitinib is avidly bound, was able to capture total and free erdafitinib plasma concentration profiles. Erdafitinib pharmacokinetics were described with a three-compartment linear disposition model with a first-order absorption process. The unbound fraction was related to the amount of AGP in a hyperbolic fashion, determined by the dissociation constant, Kd. Both total and free concentrations were modelled simultaneously but the model was expressed in terms of total concentrations. Predefined PK parameters were made dependent of the unbound fraction according to distribution hypotheses specific to the compound, i.e. that only free drug was able to distribute and that nonlinear binding to AGP only occured in the central compartment. Free concentrations were linked to total concentrations using the free fraction. Differences in AGP binding were able to account for PK differences between healthy volunteers and patients. The time course of phosphate was linearly related to erdafitinib unbound plasma concentration at biophase and enabled an accurate description of phosphate levels at the different dosing regimens. Extensive model-based simulations were performed and indicated that a starting dose of 8 mg QD using a continuous regimen, with serum phosphate measurement on Day 14 to guide potential individualized up (9 mg) or down (6 mg) titration, will maximize the proportion of patients achieving the target phosphate level (>5.5 mg/dL) while avoiding dose interruptions due to hyperphosphatemia.

Conclusions:

The PKPD modelling and simulation approach developed was used to guide selection of the optimal erdafitinib dosing regimen. Bladder cancer patients enrolled in the ongoing Phase 2 and Phase 3 studies are currently receiving the optimized daily dosing regimen, with individualization of each patient's dose based on their measured phosphate levels.

III-74: *Erwin Dreesen* Development of a population pharmacokinetic and pharmacodynamic model to describe the effect of infliximab induction therapy on mucosal healing in patients with ulcerative colitis

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Objectives: Infliximab (IFX) is a chimeric monoclonal antibody that neutralizes the pro-inflammatory cytokine tumour necrosis factor alpha. Intravenous administration of IFX following an induction scheme of 5 mg/kg body weight at days 0, 14 and 42 has been shown to induce mucosal healing (MH) in 61% of patients with ulcerative colitis at day 56[1]. A positive association between IFX serum concentrations during induction therapy and post-induction MH (between day 56 and 98) has been reported[2,3].

In this study, we applied nonlinear mixed effects methodology to compare potential exposure targets for prediction of MH.

Methods: In this retrospective, single-centre cohort study, IFX was quantified in serum trough samples during induction therapy (2000-2013)[3,4]. An endoscopy was performed before start of IFX therapy (baseline) and after two to four induction doses (post-induction, between day 40 and 100). The Mayo endoscopic sub-score was assessed and simplified to three states: 3 (severe disease), 2 (moderate disease) and 1/0 (inactive disease). MH was defined as a post-induction sub-score being ≤1 in patients with ≥2 before IFX. We assumed that only ordered transitions can occur (i.e., patients going from 3 to 1/0 transitioned through state 2 and vice versa) and that the transition probabilities between states can be inversed (eg P32=1-P23). The pharmacokinetic (PK) and pharmacodynamic (PD) models were developed sequentially in NONMEM 7.3.

Results: A total of 204 patients was available for the PK analysis of IFX and 172 patients contributed to the PD analysis (fractions at baseline sub-score state 3, 2 and 1 were 49%, 47% and 4%, resp.). A one-compartment model described the concentration time course of IFX. Serum albumin concentration (SAC) and post-induction sub-score were identified as covariates. Volume of distribution (V) was 8.1/(SAC/43) L (CV=35%), elimination rate constant (Ke) was 0.045 day^{-1} in patients with post-induction sub-score ≤1 and 0.062 day^{-1} in patients with post-induction sub-score ≥2) (CV=23%). Body weight was not identified as a covariate in this adult cohort. Individual estimates from the base model without covariates and with between- and within-subject variability on Ke (CV = 39% and 22%, resp.) and V (CV = 42% and 15%, resp.) were used as an input for the PD model. A logistic regression model described the relation between exposure and probability of achieving MH. The three observed states and six transitions were described using four parameters: the baseline proportions of patients displaying sub-scores 2 and 3, P3(t0) and P2(t0), and the times or exposures corresponding to a 50% probability of going from state 3 to 2 and 2 to 1/0. Cumulative area under the curve (CAUC) up to time of endoscopy was identified as the most relevant predictor of MH (lowest Akaike information criterion, AIC), followed by the trough concentration at day 14 (**Table 1**). X_{50} refers to the value of the metric yielding a 50% probability of conversion from 3 to 2 and 2 to 1/0.

Table 1

Modelling hypothesis	AIC	X_{50} estimates ±SE
Null model; no effect of dose, time or exposure	639	-
Cumulative dose (CD) to time of assessment drives response	637	$CD_{50}^{3->2}$ = 265 ±50 mg
		$CD_{50}^{2->1/0}$ = 739 ±118 mg
Time of assessment (T) drives response	628	$T_{50}^{3->2}$ = 16 ±3 day
		$T_{50}^{2->1/0}$ = 47 ±8 day
IFX concentration at day 14 (C14) drives response	614	$C14_{50}^{3->2}$ = 4.3 ±0.8 µg/mL
		$C14_{50}^{2->1/0}$ = 13.7 ±2.3 µg/mL
IFX CAUC drives response	601	$CAUC_{50}^{3->2}$ = 458 ±87 µg/mL*day
		$CAUC_{50}^{2->1/0}$ = 1,460 ±234 µg/mL*day

Conclusions: CAUC up to time of endoscopy is the best predictor of MH. Given the fixed induction time schedule, aiming at MH in 70% of patients and assuming time of assessment at day 84, we recommend a target $CAUC_{day\ 84}$ of 4,380 µg/L*day. Dose optimization towards this PK target can improve effectiveness of IFX induction therapy in patients with ulcerative colitis (Faelens et al., submitted, PAGE 2018).

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III-75: *Vincent Dubois* Comparative attributes of a semimechanistic and an empirical population PK model for durvalumab, a fully human anti-PD-L1 monoclonal antibody

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Background: All anti-PD1/PD-L1 monoclonal antibodies approved in immuno-oncology (IO) utilized an empirical time-varying CL population PK model to inform their labelling [1]. Limitations surrounding the use of such model were recently highlighted [2] and a more mechanistic model was proposed to delineate the gradual increase of drug exposure observed over time in cancer patients benefiting from IO therapy. However, a quantitative evaluation of the relative performance of these two alternative models was not formally conducted.

Objectives: The objective of this analysis and subsequent simulation framework was to qualitatively and quantitatively compare a recently proposed semimechanistic PK model and an empirical counterpart model.

Methods: Two candidate population PK models [2,3] of durvalumab, a fully human anti-PD-L1 monoclonal antibody recently approved in urothelial carcinoma and stage III non-small cell lung cancer, were developed in NONMEM, version 7.3.0, based on clinical data from 2 trials (NCT01693562, NCT02087423) that comprised a pool of 1409 patients with solid tumors and 7407 PK observations. Dose levels ranged from IV infusion of 0.1 to 20 mg/kg administered either bi-weekly, every 3 weeks, or monthly. Duration of therapy was limited to 12-month or contingent on clinical benefit or until unacceptable toxicity. Both models shared common aspects (a two-compartment structural form with both linear and non-linear clearances, banded-matrix stochastic model, and identical pool of statistically significant covariates, identified by stepwise covariate modelling (SCM)[4]), but differed in the implementation of the time-course of durvalumab non-specific clearance mechanisms. While the empirical model relied on a sigmoid Tmax-type model to mimic the decrease in clearance over time, the semimechanistic model associated durvalumab CL with longitudinal (not only baseline) biomarker patients' individual data. A comparison of model statistical fit, parameters and precision estimates, predictive performance (VPCs), and simulation performance was undertaken through Monte-Carlo simulations based on bootstrap replicates from both models. Since simulations of longitudinal biomarkers were necessary to derive the semimechanistic model CL time-course, a simplistic nonlinear fixed-effects modeling of longitudinal biomarker data was performed in R, version 3.3.1.

Results: Durvalumab exhibited non-linear PK with saturable target-mediated clearance at doses 50 with a typical estimate of 173 days [95%CI: 74.2; 395]. Data supported individualization of T_{max} (ω^2=0.0548), but this parameter suffered from high η-shrinkage (67%). Population PK analysis identified several statistically significant covariates that were however not clinically relevant, including body weight, sex, serum albumin, tumor size, post-baseline antidrug antibodies, creatinine clearance, ECOG performance status, and soluble PD-L1 levels [2]. Overall, the statistical fit in NONMEM (ΔOFV=-368), parsimony principle (4 less degrees of freedom), and predictive performance favoured the semimechanistic model over the empirical model. Simulations depicting the time-course of CL across replicated trials confirmed that the semimechanistic model, in addition to not being trial or trial duration dependent, provided more certain CL predictions.

Conclusion: A semimechanistic population PK model of durvalumab incorporating longitudinal biomarker in cancer patients provides superior predictive capabilities than a well-established empirical time-varying CL model, and supports the hypothesis that patients benefiting from therapy have reduced proteolytic catabolism.

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III-76: *Miro Eigenmann* Dynamic in vitro PKPD assessment to improve pharmacological response profiling of T-cell bispecifics

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Objectives: The approach for First-in-Human dose selection for cancer immunotherapy is typically based on minimally-anticipated biological effect level (MABEL) using in vitro data. A recent review by the FDA highlights that these in vitro experiments, conducted as single time measurements result into broad ranges of EC50 values and can vary under different assay conditions [1]. Response to immuno-oncology treatment is complex and includes series of events such as tumour-cell killing, cytokine release and T-cell activation which can be related to efficacy and safety of the drug. In such a complex network, these effects, however, often occur on different time scales which may lead to a bias when two readouts are quantitatively compared based on a static readout. This subsequently leads to uncertainty and inaccuracy in a derived MABEL dose prediction. Therefore more mechanistic means are needed for a better translation from in vitro to human. Here, we compare the performance of a static and dynamic in vitro PKPD assessment for CEA-TCB, a T-Cell-Bispecific Monoclonal Antibody targeting the carcinoembryonic antigen [2]. We outline how experiments and subsequent data analysis can be performed in order to get a more robust assessment of the drug's potency on various pharmacological readouts which are relevant for human dose selection.

Methods: CEA expressing tumour cell lines MKN45 (CEA high) and CX1 (CEA low) were co-cultured with human PBMCs (peripheral blood mononuclear cells) at different drug concentrations. A dynamic in vitro assay was conducted where tumour cell killing, immuno-phenotyping and cytokine release was assessed over time at 24, 48, 72, 96 and 168h. Tumour cell killing was measured by FACS and LDH release. Immuno-phenotyping of CD4 and CD8 T-cells are performed by FACS while cytokine release (IL2/6/10, IFNμ, TNFα, …) was assessed by cytometric bead array. PKPD analysis was conducted using Phoenix WinNonlin. An Emax model was fitted first to the static data where effect over concentration was evaluated at each time point. In a second step the AUCE (Area under the curve of the effect) was calculated for each concentration level and an Emax model was fitted based on the AUCE over concentration profiles for each PD readout. Derived EC50s, time course of the different PD readouts and results of the static vs. dynamic approach were compared. Potency comparison on tumour cell killing and IL6 release was proposed to explore the therapeutic index of the drug.

Results: CD4 and CD8 T-cells expand in a timely delayed manner around 48h after drug is added to the suspension. Combined with tumour cell killing over time this leads to an increase of the effector-/target cell ratio (E/T-ratio) over time. EC50 for IL2 secretion is lowest when estimated at 24h but is not identifiable after 48h as IL2 has been consumed in the system by that time. Lowest EC50 values for IL6 release are found at later times, after 96 hours. Also for tumour cell killing EC50 estimates are lower at later times, whereas they are consistently lower than EC50s for IL6 at all times. As readout for the therapeutic index, we computed the ratio of EC50 of IL6 as a potential marker for safety over the EC50 of tumour killing efficacy readout. Here, dynamic in vitro PKPD predicts a therapeutic index of 150, while this assessment with the static analysis leads to indices ranging from 5 to 130. These findings demonstrate that estimating EC50s based on a static in vitro readout is variable across different time points and appears unreliable.

Conclusions: Our results indicate that a comparison of the drug's effect on different PD readouts occurring at different time scales is not meaningful. This can be circumvented when considering the full time course in the PKPD analysis such as relating the integral of the time course of the effect (AUCE) versus concentration to derive the potency. The relevant time span thereby depends on the time when the effect comes into play during the complex cascade of immune response and T-cell mediated tumour killing. Further integrating such dynamic in vitro data into a systems pharmacology framework will help to better understand the mechanics behind tumour lysis and immune response upon treatment with TCBs as function for target expression and drug-target interaction. Progressing in the understanding of this complex system will eventually enable a refined MABEL approach and a better in vitro-in vivo extrapolation.

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III-77: *Salvatore D'Agate* Development of a drug-disease model describing individual IPSS trajectories in BPH patients: Implication of disease progression and covariate factors on long term treatment response

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Objectives: Lower Urinary Tract Symptoms (LUTS) caused by Benign Prostatic Hyperplasia (BPH) are typically measured by the International Prostate Symptom Score validated questionnaire. The IPSS provides information on LUTS improvement as well as deterioration, the last being the key outcome of BPH progression. While most of the available evidence refers to mean or median changes, little attention has been given to individual IPSS trajectories [1,2]. The current investigation aimed to develop and validate a drug-disease model describing individual IPSS trajectories in moderate and severe LUTS/BPH patients receiving placebo, dutasteride, tamsulosin or combination treatment. Clinical trial simulations were then performed to demonstrate the impact of the underlying disease progression and covariate factors on the deterioration of symptoms, disentangling it from the drug effects.

Methods: A meta-analytical approach was used including pooled data from moderate and severe LUTS/BPH patients (N=10238) enrolled into six clinical studies [3-6]. For consistency and standardization purposes, baseline measurements were defined as those collected on the last day of the placebo run-in phase. To ensure that patient and disease-specific fluctuations in IPSS trajectory were disentangled from treatment-specific changes, individuals treated with placebo only were used for model development. Watchful waiting was considered as a non-pharmacological intervention and handled as an active treatment arm. A nonlinear mixed effects model was developed using NONMEM v7.2, in which disease specific characteristics were parameterised independently from drug effects; consequently, treatment response was then evaluated as a covariate effect on the underlying disease model parameters. Standard graphical and statistical methods were used for model building, covariate selection and evaluation. A sensitivity analysis was subsequently performed using the final model to investigate how individual parameter estimates, treatment and covariate factors affect individual IPSS trajectories. Predictive performance was assessed using internal and external validation procedures.

Individual IPSS vs time profiles were simulated for a virtual BPH population including baseline characteristics resampled from the original clinical studies. Mean profiles along with 95%-CI were used to illustrate the effect of different treatments in patients with varying rates of disease progression. Results were summarised based on the predicted absolute change in IPSS at predefined visits. For the purposes of these simulations, clinical response was defined as improvement in IPSS ≥25% relative to baseline.

Results: Despite considerable noise and interindividual variability in IPSS measurements, improvement and deterioration of IPSS was characterized by a Gompertz function. Covariate factors (namely, baseline IPSS, BMI, duration of symptoms and alcohol user status) were found to affect both the parameters describing the disease progression and placebo effect. Interindividual variability was identified for the parameters describing the zero-order disease progression parameter as well as the magnitude and half-life of placebo effect. Residual variability in IPSS was described by a proportional and additive error model.

Exploratory simulations showed that treatment response depends on the underlying disease progression rate and baseline IPSS, making it difficult to distinguish the contribution of each factor to the response. Our results also indicate that individual IPSS trajectories can be predicted over the course of treatment and may be clustered according to the underlying rate of disease progression (i.e., fast, moderate, slow progressing phenotypes). No independent prognostic baseline factor could be identified that can be used as a predictor of response or the time course of symptoms.

Conclusion: Individual IPSS trajectories can be characterised by a longitudinal model. In addition to the identification of baseline covariates, the use of a longitudinal model enables characterization of the initial improvement followed by slowly progressive changes in IPSS. Initial simulations shed further light into the factors that explain interindividual differences in the rate of disease progression and consequently in the deterioration of symptoms.

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IV-01: *Brigitte Lacroix* A quantitative framework integrating exposure, efficacy, receptor occupancy and tolerability to propose evidence-based dose regimens for padsevonil

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Objectives: To develop a quantitative framework integrating pharmacokinetics (PK), receptor occupancy (RO), clinical outcome (PKPD) and tolerability data at the end of the proof of concept (PoC) phase II study, with the intention to propose a rational dose regimen selection for further development of padsevonil (PSL) in drug resistant patients with epilepsy.

Methods: Data from two clinical studies were used to develop the framework: the PoC study and a Positron Emission Tomography (PET) study for SV2A receptor occupancy. The modeling of the PK, clinical outcome PKPD and tolerability PKPD was based on data from the PoC study in 55 drug resistant patients with epilepsy receiving 400 mg bid. A population PK (popPK) model was developed based on rich sampling on 2 dosing occasions and sparse PK samples. The individual predicted daily average PSL plasma concentration obtained from the popPK model (Cavg) was integrated in the PKPD model describing the longitudinal daily seizure count data. The PKPD for tolerability was explored linking the Cavg with the treatment emergent adverse events registered as scores grouped in three categories: psychiatric disorders, nervous system disorders and a combination of the most relevant nervous system disorders and some general disorders such as "fatigue" and "gait disturbance". The tolerability data were analyzed using a proportional odds model assuming consecutive scores to be highly correlated. The modeling of SV2A RO was based on data from a PET study in 11 healthy subjects who received various single doses of PSL (6.25 to 100 mg). Simulations were performed from the popPK model and the RO model, that were combined with the outcome from the PKPD model (estimated daily average concentration to reach 50% of maximum reduction in seizure count), the outcome of the PKPD tolerability model. Additionally, the expected GABAa receptor occupancy from a previous study was used to inform the modelling outcome in order integrate all information and propose dosing regimens for the further clinical development of Padsevonil.

Results: The PK of PSL was described by a 2-compartment model with first order absorption and first order elimination from the central compartment. An Emax model described the SV2A receptor occupancy as a function of PSL plasma concentration at the time of the PET scan where the EC50 was estimated at 3.1 ng/mL and EC90 at 27.9 ng/mL. The PSL effect on seizure reduction was described using a negative binomial distribution, taking previous-day seizure frequency into account. Baseline seizure rate was estimated at 1.3 day^{-1}, placebo effect at 20% and EC50 at 190.6 ng/mL. A bi-modal distribution was used to separate the population into responders and non-responders, with almost 45% of the patients allocated to the responder group in this drug resistant epilepsy population. The PKPD model for tolerability showed that the probability of moderate to severe adverse events for patients treated with doses lower than 200 mg bid are similar to that of patients treated with placebo. No adverse-event dose dependency was evident when comparing 200 mg to 400 mg bid. Simulations of the PSL PK profiles at doses of 100 mg to 400 mg bid showed that the plasma concentration profiles after intake of 400 or 300 mg overlap largely. At 300 and 400 mg doses, the predicted concentrations remain above the EC90 for SV2A RO over the whole dosing interval at steady-state. At 100 mg bid, about 75% of the population is predicted to remain above EC90 at Ctrough.

Conclusions: An integrated approach has been used to project dose recommendations, using a combination of PET RO-exposure analysis, a population PK model and PK/efficacy effect estimation. Overall the analysis results allowed identification of doses proposed for further clinical development of PSL, including 400 mg bid as a top dose associated with >90% sustained SV2A RO in the entire population and quantifiable GABAa RO, and 100 mg bid as a low dose associated with >90% SV2A RO and lack of quantifiable GABAa RO.

IV-02: *Shankar Lanke* Population Pharmacokinetic Analyses of Tolvaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease

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Objectives: Tolvaptan has been shown to slow the progression of kidney enlargement and the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD) [1]. The objective is to develop a population pharmacokinetic (Pop PK) model to describe tolvaptan pharmacokinetics in ADPKD subjects following oral administration.

Methods: Pop PK analysis included data from 1091 subjects with 7335 observations split into dense and sparse data. The Pop PK model was developed using NONMEM version 7.3.0 and the stochastic approximation expectation maximization estimation method. A one and two compartmental models (CM) with first and zero order absorption, first-order elimination were evaluated to determine the structural model. Full covariate analysis was conducted to evaluate the effects of covariates on PK parameters. Final model was qualified using visual predictive check (VPC), 500 data sets were simulated. The model stability was assessed by a 1000-run bootstrap analysis.

Results: PK was best described by a one CM with zero-order absorption, non-linear relative bioavailability (F1) and first-order elimination. Step-wise and non-linear effect approaches were tested to investigate the effect of dose on tolvaptan F1. A non-linear F1 significantly improved the model with a decrease in objective function value by 132 points. As dose increased from 15 mg to 120 mg, F1 decreased by 36%. Population estimates for CL/F, Vc/F, duration of absorption (D1), the amount of drug at which F1 is minimum (Vmax) and the amount of drug at which F1 is 50% (km) were: 12.6 $L \cdot h^{-1}$, 110 L, 0.589 h, 182 mg and 166 mg respectively. The inter-individual variability was 64% in CL/F, 70% in Vc/F, 238% in D1. Residual variability was described by a combined error model.

Covariate analysis revealed the following effects:

- Tolvaptan CL/F decreased with decrease in eGFR. An eGFR decrease from 69.39 (median value) to 32.47 (mL/min/1.73 m2) would result in a 33% reduction in CL/F ie, from 12.6 L/h to 8.4 L/h. Consequently, leading to higher exposures in subjects with low eGFR.
- In a previous dedicated drug-drug interaction study conducted in healthy subjects, it was observed that subjects on strong CYP3A4 inhibitor (ketoconazole 30 mg) had a 3.5- and 5.4-fold increase in Cmax and AUC_{∞}, respectively, as compared to subjects not taking CYP3A4 inhibitor [2]. Based on the current analysis, co-administration of CYP3A4 inhibitors with tolvaptan reduced CL/F by 22%; this relatively small effect was observed as most of the patients were on weak CYP3A4 inhibitors.
- Tolvaptan CL/F decreased with increased body WT. The impact of WT on CL/F ranged from -17% (for a 42.3 kg) to +21% (for 113 kg) of the typical value.
- Tolvaptan Vc/F increased with increased body WT. The impact of WT on Vc/F ranged from -8% (for a 42.3 kg) to +8% (for a113 kg) of the typical value 110 L.

The VPC plots showed acceptable model predictive performance across all dose regimens, few peak tolvaptan plasma concentrations were outside 90% CI. Some of these observations may have been captured by the model if dosing in the fasted or fed state had been able to be incorporated as a covariate.

As tolvaptan dose is increased from 30 to 90 mg, Cmax values are increased 15 to 96% when tolvaptan is dosed following a high-fat meal [3,4,5]. Dosing in the fasted or fed state was not captured in the database.

The Pop PK model developed is stable with 99.7% successful bootstrap runs.

Conclusions: Tolvaptan PK was well described by a one CM with eGFR and co-administration of CYP3A4 inhibitors as a significant covariates on CL/F.

For the treatment of ADPKD, dosing is initiated at 45 mg upon waking and prior to a meal and 15 mg about 8 hours later. Subjects should be up-titrated to 60/30 mg and 90/30 mg depending on tolerability. Increases in daily urine volume following tolvaptan are lower as eGFR decreases [6,7] despite the increases seen in tolvaptan concentrations, thus increasing subjects' tolerability to aquaretic side effects [8]. Dose reductions to 30 mg or 15 mg once daily, depending on tolerated dose, is recommended when tolvaptan has to be administered with a potent CYP3A4 inhibitor [1].

The model is stable and acceptable, so an external validation will be performed using data from an independent trial conducted in ADPKD patients. This model will be used to obtain individual exposures for an independent study to develop a PKPD model.

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IV-03: *Christian Laveille* Population pharmacokinetics of Rimeporide in healthy volunteers and children suffering from Duchenne Muscular Dystrophy (DMD)

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Objectives:

Duchenne Muscular Dystrophy (DMD) is a rare genetic disorder characterized by the progressive loss and degeneration of skeletal and cardiac muscles affecting boys [1]. Mutations in the dystrophin gene lead to disease by preventing the expression of dystrophin, a structural component in muscle tissue. The lack of the dystrophin protein leads to membrane instability and uncontrolled intracellular homeostasis including calcium which accumulation contributes to the disease [2].

NHE-1 (sodium-hydrogen exchanger type 1) is a key membrane transporter regulating intracellular Na^+ concentration and pH by catalysing the electroneutral counter transport of Na^+ and H^+ through the plasma membrane [3]. The NHE-1 isoform is ubiquitous and is present on muscle fibers. When activated, it leads to a significant increase in intracellular Na^+ triggering an intracellular Ca^{2+} overload through the Na/Ca exchanger. Therefore, inhibiting NHE-1 transporters can regulate intracellular Na^+ and Ca^{2+}.

Rimeporide is a potent and selective NHE-1 inhibitor which has been shown to be cardioprotective and to improve skeletal muscle phenotype in animal models of DMD. A previously reported pharmacokinetic model [4] was built based on healthy adult data in order to simulate Rimeporide concentrations in young boys suffering from DMD.

The aim of this work was to refine the existing Rimeporide PK model after pooling the data coming from these adult healthy volunteers studies and from a clinical study in paediatric DMD patients.

Methods:

Rimeporide plasma concentrations after intravenous and oral administrations obtained from 6 clinical studies in adult healthy volunteers and from one phase Ib study in children with DMD were pooled for the analysis. In total, plasma samples from 176 individuals (156 adults and 20 children from 6 to 11 years) after administrations of Rimeporide at different dose levels and dosing regimen were available for the analysis.

Available covariates were: age, ALT, AST, bilirubin, BMI, body weight, glomerular filtration rate, dose, food, lean body weight, serum creatinine and cystatin C (DMD disease impacting serum creatinine values, Cystatin C was used instead for computation of the glomerular filtration rate).

The modelling exercise was performed using the FOCE-I method implemented in NONMEM 7.3 and model development was guided by residual- and simulation-based diagnostics.

Results:

The refined population PK model to describe Rimeporide concentrations was a three-compartment disposition model with an absorption phase described by multiple transit compartments and a first-order elimination process.

A stepwise covariate modelling analysis revealed that the absorption rate was lower in fed condition (~50% lower) and clearance decreased when GFR was low ()a reduction of 20% was found in indivudla with the lowest GFR compared to a typical individual), confirming the elimination pathway of Rimeporide.

Incorporation of serum creatinine levels on distribution process was found to be better than bodyweight in order to explain both adults and DMD children, indicating that Rimeporide might be distributed in muscle tissues (body composition being altered in DMD disease with a loss of muscle mass). A reduction of 25% was found on the individual volume of distribution in the child with the lowest value of serum creatinine compared to a typical individual with a serum creatinine level of 115 µmol/L.

Model evaluation by goodness-of-fit and pred-corrected Visual Predictive Check were satisfactory.

Conclusion:

The presented PK model built from both adult healthy volunteers and young boys suffering from DMD studies described satisfactorily the Rimeporide data. The Rimeporide PK model will be expanded to investigate potential relationships between Rimeporide concentrations and muscle damage biomarkers as they will be available.

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IV-05: *Robert Leary* Automatic framework for bioequivalence studies from In Vitro test to In Vivo study design

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Objectives: The traditional deconvolution-based method of in vitro-in vivo correlation (IVIVC) for bioequivalence (BE) studies pre-dates modern population approaches to PK modeling. For example, it does not incorporate inter-individual (IIV) and inter-occasion variability (IOV), is limited to linear one and two compartment models, and does not accommodate study protocols based on clinical trial simulation such as parallel, crossover and replicate designs. It is not flexible enough and sufficiently free from bias to meet all the requirements in BE studies such as single dose, multiple doses (steady-state) and food effects. Hence the IVIVC method has not been widely used for human BE studies and Abbreviated New Drug Applications (ANDAs) based on IVIVC are rarely successful [1]. This project is intended to create an automatic framework that addresses the deconvolution-based limitations and provide a user-friendly automatic methodology to help BE studies from in vitro test identification to in vivo study design and thus facilitate improved bioequivalence strategies for more timely approval of ADNAs.

Methods: The automatic framework can be described in different stages including before BE studies, after BE studies, and after pilot studies. The relationship between these stages includes the following.

A direct IVIVC model incorporating a pharmacokinetic PK model (D-IVIVC-PK) is created [2], including steps:

1. Selection of a dissolution function from a candidate set such as Hill, cumulative Weibull, cumulative double Weibull, Hiquchi, Makoid-Banakar, Kopcha, or user-provided custom function, to best fit (e.g, according to AIC) the in vitro dissolution data.
2. Differentiation of the in vitro function for use as a forcing function in a differential equation-based IVIVC and PK model.
3. Collection of all relevant in vivo data such as single dose (IV & oral), multiple dose, food effects, including covariates and formulations (categorical covariates as well as IOV) for use in an NLME model, with any possible variabilities such as IIV, IOV, or sequence effect, period effect, formulation effect or carryover effect.
4. Nonlinear mixed effect modeling (NLME) for model estimation to fit the in vivo plasma/blood data.
5. Model diagnostics and model evaluation reporting, such as VPC, OFV etc.

This model is used to support clinical trial simulation (CTS) and the required bioequivalence ANOVA test, including:

1. Use of the fitted D-IVIVC-PK model for simulation and study design including parallel, crossover and replicates design
2. Computation of PK parameters such as Cmax, Tmax, AUC as well as other relevant secondary parameters and information such as sequence, subject, period, formation
3. A variety of possible bioequivalence studies are created accommodating features such as single dose, multiple dose and food effects.
4. AVOVA test is provided for average, population and individual bioequivalence test

In vitro test experiment support includes:

1. Automatic comparison from a list of in vitro dissolution tests on the reference formulation (e.g. different pH, volumes, media type, rotation speed, USP etc.) from the above D-IVIVC-PK models
2. Ranking the list of in vitro dissolution methods and using the best in vitro dissolution test for the clinical trial simulation and design
3. Both reference and test formulation are used for the above CTS and BE test to determine the likely success of test formulation

Ideally, IVIVC can serve as a surrogate for human BE studies includes:

1. Collection of all the test formulations (such as slow, median/reference and fast release) in vitro dissolution data and in vivo human data together to build D-IVIVC-PK model as above
2. Validation of data for each formulation can be performed via standard model diagnostics
3. A new test formulation is used for the above CTS and BE ANOVA test by comparing with the reference formulation

R**esults:** By selecting a few options and a few clicks from a user-friendly screen, a user can follow the automatic framework to make the best decision for formulation strategies as well as bioequivalence strategies.

Conclusions: The built automatic framework for BE studies can save resources and get more timely approval from ADNAs. This automatic framework also helps generic pharma companies eliminate common mistakes and provides a step-by-step work-flow easy for regulatory ADNA assessment.

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IV-06: *Woo Yul Lee* A population pharmacodynamic model of combination antidepressant therapy in depression

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Introduction: We believe only few population pharmacodynamic models have been developed regarding clinical effects of an antidepressant. Moreover, in real clinical settings, it is prevalent to use antidepressants in multiple categories as combination regimen to improve depressive symptoms rather than a single category regimen. In this respect, it is essential to estimate the effects of drugs prescribed for depression including antidepressants, antipsychotics, mood stabilizers and anxiolytics from different category and quantify expected beneficial effects when used as a combination therapy.

Objectives:

- Develop a pharmacodynamic model of frequently used antidepressants

Methods: MADRS (Montgomery Asberg Depression Rating Scales) were used for the measurement of drug effect on depression [1] and our data were collected retrospectively using Electric Medical Record in Yonsei university hospital from January 2005 to August 2017. Patients who were hospitalized for depression, major depressive disorder and depressive disorder as main diagnosis were included in our data. The total number of subjects and measurements used for analysis were 129 and 353, respectively. MADRS score was measured at the time of admission and few days later for follow up score after treatment. The number of MADRS score measured in each individual ranged from 1 to 8. Classes of drugs of interest were SSRI, antipsychotics, benzodiazepines, tetracyclic antidepressants, mood stabilizers and buspirone. Each was administered on daily basis until the day of discharge, so we could assumed all had reached steady state concentration at the time of follow up measure of MADRS score even though there were no concentration records. Data exploration and model building process was carried out using R ver 3.3.3 and NONMEM ver 7.3.

Results: Mixed weibull model was chosen for the basic structural model [2]. Based on the structural model, Effects of antidepressants on the MADRS score were 0.031 (SSRIs), 0.016 (antipsychotics), 0.0215 (benzodiazepines), 0.047 (tetracyclic antidepressant), 0.0513 (buspirone) and fixed to be 0 which was less than 0.001 (mood stabilizers). Buspirone showed the largest effect on MADRS score improvement. Estimated baseline score for MADRS score was 28.6, and hill coefficient that explains the curvilinearity of descending MADRS score was 0.37. . The inter-individual variabilities (CV%) were 29.72% (SSRI), 31.47% (antipsychotics), 30.65% (benzodiazepines), 32.89% (tetracyclic antidepressant), 14.02% (baseline MADRS score). We fixed CVs for other parameters to be 0 due to high eta shrinkage and statistically insignificant value. Relative standard errors (RSEs) in parameters ranged between 46% and 62% for the effect of drugs and those in other parameters were less than 34%.

Conclusions: We started to quantify the effect of each drug in combination regimen. The model will further be developed with potential covariates, and inter-occasional variabilities so we can predict and suggest optimized antidepressant combination therapy in patient with depressive symptoms.

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IV-07: *Quentin Leirens* Clinical Trial Simulation of a Phase I Paediatric Oncology Study using Simulo

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Introduction: The main challenge during oncology drug development in the paediatric population is to improve the clinical development process making it faster to have access to safer and more effective treatments. Dose-finding studies in paediatrics have to be designed to avoid a large number of patients being treated with ineffective doses and, at the same time, to avoid overdosed patients. Regulatory agencies advocate the use of modelling and simulation of the available adult data to guide paediatric clinical trial designs [1,2]. One of the most intuitive and user-friendly software for performing clinical trial simulations is Simulo [3], a Java-based application running on an R backend with a graphical user interface. In Simulo it is easy to define the design of a paediatric clinical study and simulate using model parameters derived from adults and the body weight and age distribution for children.

Objectives: To show the capabilities of Simulo for simulating a paediatric phase I oncology clinical trial with the aim to predict a dose level that likely provides a similar exposure range as in adults. For this illustrative clinical trial simulation example, we selected to predict the potential outcome of an ongoing study [4] with trametinib, a MEK inhibitor approved in adult population for the treatment of V600E or V600K BRAF mutation-positive melanoma.

Methods: A previously developed population pharmacokinetic model for trametinib in adult patients [5] was implemented in Simulo. Simulations of the paediatric population were performed using the adult pharmacokinetic model, allometric scaling, and paediatric body weights sampled from the NHANES database [6], corresponding to children from 2 to 17 years. Three dose levels were simulated (0.0125 mg/kg, 0.025 mg/kg, and 0.040 mg/kg) in accordance with the ongoing clinical trial [6]. A total of 18000 different paediatric patients were simulated in order to generate 1000 virtual clinical trials, consisting of 6 patients per clinical trial and dose level. The percentage of "successful" trials under each dose level was defined as the fraction of 1000 virtual trials with exposure related parameters ($AUC_{0\text{-}24,ss}$, $C_{min,ss}$, and $C_{max,ss}$) within the corresponding adult geometric mean value ± 20%. Moreover, the 90% prediction interval (PI) of adult exposures after 2 mg daily was generated by simulating 6000 profiles using the adult population pharmacokinetic model. The percentage of virtual paediatric clinicals trials where 6 out 6 patients were within the corresponding interval was then calculated.

Results: At the lowest dose of 0.0125 mg/kg, 100% of the simulated clinical trials were below the exposure targets for all three metrics. With the intermediate dose level, 23% of the simulated clinical trials had a $C_{min,ss}$≥10 ng/mL (trough plasma concentration that has been found to be associated with progression free survival in an adult exposure-response analysis [5]), and none of the virtual trials were above the upper limit for the corresponding $C_{max,ss}$ in adults. For the highest dose level (0.040 mg/kg), an $AUC_{0\text{-}24,ss}$ above the upper limit was found in 42% of the virtual trials and more than 44% would have $C_{min,ss}$≥14 ng/mL. For the intermediate dose only 29 %, 31% and 45% of virtual paediatric trials showed that 6 out of 6 patients were within the 90% PI of the adult $AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and $C_{min,ss}$ reference ranges, respectively.

Conclusions: Application of modelling and simulation using the previous knowledge from adult populations can help to explore different scenarios before enrolling paediatric patients into phase I clinical trials in order to avoid treatment with ineffective dose levels and to define the most convenient dose in a faster

way. Other parameters like the number of children to be enrolled, different dosing strategies (flat dosing or tier-based dosing), can be also easily simulated using Simulo.

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IV-08: *Jennifer Leohr* A Categorical Model of Sweet/Fat Preference Taste in Lean, Obese and Very Obese Subjects

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Introduction/Objectives: Obesity is a disorder of chronic positive energy balance, whereby excess of energy intake beyond energy utilization leads to an increase in adipose tissue. Chronic over-eating leading to the development of obesity can be modeled as an addictive behavior similar to other substance disorders in which craving and reward play a key role. In a series of studies assessing hedonic response and preference for dairy solutions with varying sucrose and fat content, the degree of hedonic response elicited by preferred solutions was shown to be related to weight gain [1] and the corresponding preferred sugar to fat ratio was shown to vary with BMI [2]. The aim of this study was to assess the hedonic response to dairy solutions with variable concentrations of sucrose and fat were measured as a surrogate for sensitivity to reward and to determine relative preference for sweet and fat in normal-weight versus obese subjects.

Methods: Data was collected from a single-center, in a total of 64 subjects, roughly 20 subjects in each of the three population categories based on BMI: lean (18.5-24.9), obese (30-33), and very obese (34-40). Approximately 90 minutes following the lunch meal, subjects will undergo a sweet and fat taste preference test. For example, subjects may be presented with 16 randomly ordered solutions of skim milk (0% fat), whole milk (3.5% fat), half and half (11.3% fat) and cream (37.5% fat) each containing 0%, 5%, 10%, or 20% sugar by weight. Subjects rated solutions for sweetness, creaminess and pleasantness on three separate scales anchored with descriptors of “not at all” and “extremely.” The set of solutions were rated twice. Nonlinear mixed-effect modeling was used to model the categorical data from the scoring of the sugar/fat preference test, using NONMEM® [3] and Perl-speaks-NONMEM [4] as the modeling environment.

Results: The creaminess score was well described with a proportional odds model with linear effects of sugar and fat on the score. The sweetness score was also well described with a proportional odds model. Sugar content effects on the score was best described by an Emax model. The pleasantness score was more complex than both the sweetness and creaminess score. A differential odds model allowed for the sugar to be less than proportional and fat to be greater than proportional on the score. In addition, the sugar and fat effect on pleasantness was described by an Emax model with an estimated interaction between fat and sugar.

Conclusions: The creaminess score was unsurprisingly dependent on the content of the fat in the test. In addition, the results showed that sugar amount increased the creaminess rating. Similarly, the sweetness score was dependent on the amount of sugar with the fat content increasing the sweetness rating. Population differences were identified for the baseline of sweetness. The pleasantness score was dependent on both the amount of sugar and fat content of the test, with both showing a maximum response on the score (Emax models). The interaction between sugar and fat was negative, indicating an antagonistic interaction on the pleasantness score; thus, doubling the fat content and the sugar amount will not quadruple the pleasantness. This was also observed in the raw data where higher fat content reduced the pleasantness score for all amounts of sugar. The development of this model provides a unique opportunity to further understand these complex interaction of sugar and fat on hedonic response. In

addition, this approach provides a powerful tool to conduct simulations for hypothesis testing and avoiding additional subjects enduring a tedious and time consuming test.

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IV-09: *Giulia Lestini* Two-step modelling approach of time to event and cognitive decline to inform Alzheimer's disease prevention trials

Giulia Lestini (1), Amy Racine (1), Ines Paule (1), Chrystel Feller (1), Kostas Biliouris (2), Etienne Pigeolet (1), Cristina Lopez Lopez(1), Ana Graf (1), Angelika Caputo (1)
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Objectives: Optimal clinical trial designs to evaluate innovative treatments[1] are needed to test disease-modifying interventions in the Alzheimer's disease (AD) prevention setting. The aim of our work was to develop a model to support the design of such clinical trials in participants at risk of developing mild cognitive impairment (MCI) or dementia due to AD. In particular, we wanted to assess the performance of two different endpoints in terms of statistical power. These are: i) the time to MCI or dementia diagnosis and ii) the cognitive decline, as measured by a recently developed composite cognitive score, the Alzheimer's prevention initiative preclinical composite score (APCC)[2], intended to detect subtle cognitive changes in early stages prior to MCI or dementia diagnosis.

Methods: We first developed a time to event (TTE) model describing the time to first diagnosis of MCI or dementia using parametric survival functions. The TTE model was fitted to longitudinal data from the National Alzheimer's Coordinating Center (NACC) and data collected from three cohort studies (ROS, MAP and MARS) of aging and dementia at the Rush Alzheimer's Disease Center. As a second step, mixed-effects models describing the progression of APCC scores over time were developed and fitted to two subpopulations in the Rush cohorts. A nonlinear-mixed effects model was fitted to the so named "progressors" subpopulation, i.e. subjects with first diagnosis of MCI or dementia within eight years, and a linear-mixed effects model was fitted to the "non-progressors", i.e. subjects who either were not diagnosed or had a diagnosis only after eight years.

A time scale anchored at the time to MCI or dementia diagnosis predicted by the TTE model was used for the progressors model.

Clinically relevant covariates were tested for statistical significance in both models using backward elimination based on Akaike's information criterion. The estimation of APCC and TTE models parameters was performed using the R software. Simulations based on these models were performed to assess the power of a clinical trial using either the TTE or change in the APCC as endpoints. Different scenarios assuming different treatment effects expressed in terms of hazard ratio, i.e. assuming a reduction in the risk of MCI or dementia diagnosis, were simulated.

Results: In the TTE model, a Weibull survival function performed best among several other candidate functions, and it included age and APCC at entry of the study, APOE-ε4 status, and number of years of education as covariates. Predicted survival probabilities were adequately distributed around the Kaplan-Meier survival curves derived from the observed Rush and NACC data. Moreover, relevant diagnostic plots confirmed the quality and good predictive performance of the two APCC models. Both progressors and non-progressors models included APCC at entry of the study, APOE-ε4 status, number of years of education and gender as covariates. Furthermore, the progressors model included age at event whereas the non-progressors model included age at entry of the study as covariates. Trial simulations showed that an overall power greater than 80% could be reached with a realistic hazard ratio and reasonable sample size. The

power to show a treatment effect was higher with a TTE endpoint than with a change in APCC for all tested scenarios.

Conclusions: This two-step modelling approach of time to MCI or AD diagnosis and APCC decline has been successfully used to design clinical trials in the AD prevention setting. The model shows good internal validity and allows comparing the performance of different endpoints in terms of statistical power. Further refinements of the model, e.g. including amyloid-beta and tau as covariates are objectives of future research.

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IV-10: *Leticia Arrington* A Model Based Meta-Analysis (MBMA) to support development of medicines for treatment of DPN, PHN and Fibromyalgia.

Leticia Arrington (1)*, Han Witjes (2)*, Akshita Chawla (1), Richard Franzese (2), Mark Lovern (2) and Sreeraj Macha (1)
(1) MSD (2) Certara

Objectives:

The objective of the analysis was to develop a MBMA comparator model for neuropathic pain to provide a quantitative framework for comparison of drugs commonly used for the treatment of diabetic peripheral neuropathy (dpn), post herpetic neuralgia (phn) and fibromyalgia. The following drug classes were included in the analysis: antiepileptics (AEDs), a2δ, benzodiazepine, cannabinoids, opioids, Nav 1.7, serotonin-noradrenaline reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) antidepressants, and tricyclic antidepressants. Specific objectives include development of a joint response MBMA model describing the proportion of subjects who achieved 30% (PID30) and 50% (PID50)[1,2]reduction from baseline in pain score. This MBMA platform is envisioned to help develop better neuropathic pain (NP) therapies.

Methods:

A systematic review of the literature was conducted using a predefined inclusion/exclusion criteria. The database captures publically available, summary-level clinical trial data from 121 placebo and/or active controlled randomized trials. The analysis dataset for PID30 and PID50 contained 75 trials with 22 drugs and 3 combined therapies across 9 drug classes. Model development, evaluation and simulations were performed using R 3.3.2. The models were developed using the generalized nonlinear least squares (gnls) and nonlinear mixed-effects (nlme) functions provided in R. The response in the MBMA model was described as the sum of a trial specific non-parametric (unstructured) placebo effect and a parametric drug effect depending on indication, dose, time, model parameters and covariates. Dose-response was estimated where possible, with drug specific treatment effects within indication using a shared Emax within a drug class and drug-specific potency (ED50). Fixed-effect estimates for the mean shift in placebo response on the logit scale from 50% reduction to 30% reduction and trial-specific random effects accounted for trial heterogeneity. The correlation between multiple observations within one treatment arm was accounted for by assuming a compound symmetry correlation structure for all observations within one arm within a trial. Model appropriateness was assessed using goodness of fit plots and additional simulations. Covariates were graphically explored and age, black race and baseline score were tested for statistical significance. Treatment effect estimates with associated 95% confidence intervals were derived as the mean and 2.5^{th} - 97.5^{th} percentile intervals across 3000 simulated data sets with parameter values sampled from the multivariate normal variance-covariance matrix of the estimates.

Results:

The final MBMA model shows that the magnitude of placebo response differs between indications. The estimated placebo response for PID30 is 42%, 37% and 30% for dpn, phn and fibromyalgia respectively and that for PID50 is 26%, 22% and 17%, respectively. Age was identified as a significant covariate as the PID30 and PID50 rates increased with increasing age for dpn and phn patients. All other covariates (baseline pain score, disease duration, sex, BMI, race etc) were evaluated but were not found to be significant. Treatment

effects (mean, 95% CI) were estimated from the final MBMA model and presented in forest plots to compare treatment effects of common NP drugs in DPN, PHN and Fibromyalgia.

Conclusions:

The available PID30/50 data were well described by an Emax model. Placebo response and drug effects differed markedly across indications. The model derived from this analysis will provide a quantitative framework for benchmarking new investigational compounds to SOC and improve understanding of D-R relationship for compounds used in treatment of pain.

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IV-11: *Hyeong-Seok Lim* Pharmacokinetic and Pharmacodynamic Evaluation of Intravenous Levetiracetam in Children with Epilepsy

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Objectives: This study aimed to evaluate the safety and tolerability of intravenous (IV) levetiracetam (LEV) as monotherapy in children aged 1 month to 16 years old and further to explore the pharmacokinetics (PK) of IV LEV and the time to seizure after IV and then oral administration of LEV in pediatric patient with epilepsy.

Methods: An open-label, single-arm, single centersingle-center trial for pediatric patients with epilepsy was conducted to evaluate the PK, frequency of seizure recurrence, and toxicity of IV LEV. Children diagnosed with any type of acute unprovoked seizure and requiring in-hospital IV LEV administration were included. Plasma LEV (m/z 171.0) concentrations were measured using high-performance liquid chromatography with tandem mass spectrometry after sample preparation by liquid-liquid extraction. Clinical seizure outcomes, side effects, and Korea-child behavior checklist after administration were monitored and the PK, repeated time to seizure was analyzed via modeling using NONMEM in these children. A total of 107 plasma concentrations of LEV from 37 children (median age, 4.6 years; median weight, 18.0 kg) with epilepsy who received IV LEV were used for the current PK analysis. Seizure recurrence data were collected retrospectively from a total of 34 pediatric patients in Asan Medical Center who received a single IV and then multiple oral doses of LEV during the study.

Results: The plasma LEV concentrations after IV LEV were best described by one-compartment linear PK model. Only body weight was associated with both clearance (CL) and volume of distribution (V) of LEV in the power model. Typical CL and V in children of 18 kg in body weight were, 1.44 L/h and 8.55 L, respectively. Basic goodness of fit plots and model predicted vs. observed LEV concentration plots indicated that the final PK model is reasonable. The body weight proved statistically significant in randomization tests since the minimum objective function value (MOFV) of the final PK model was a lot lower than the 2.5^{th} percentile of the MOFV distribution obtained from 1,000 datasets where the WT was randomly permuted. Weibull distribution model described the time to seizure recurrence well with estimates for scale and shape parameters of 0.01 and 0.77, respectively. In the covariate analysis, no statistically significant predictor for the time to seizure recurrence was identified. The model prediction was in good agreement with the Kaplan–Meier curve.

Conclusions: This study evaluated the PK, treatment effect and adverse events after a single IV LEV and repeated time to seizure recurrence after a single IV LEV followed by multiple oral doses of LEV in children with acute repetitive seizures or status epilepticus. The PK modeling analysis identified body weight as a covariate affecting the PK of IV LEV in children. The repeated time to event modeling analysis described the seizure recurrence over time after conventional LEV therapy in children. The current study results provide practical knowledge that applies to optimal, individualized LEV therapies in children with epilepsy.

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IV-12: *Sihang Liu* Population PK/PD analysis of ropinirole as a potential treatment for hyperprolactinemia

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Objectives: While ergoline dopamine agonists are standard therapies for the treatment of hyperprolactinemia and prolactinomas, in a subset of patients their use is limited by drug intolerance and resistance. This study aims to examine the acute effect of the non-ergot dopamine agonist ropinirole on prolactin levels in hyperprolactinemic subjects, in order to evaluate the drug's pharmacokinetic and pharmacodynamic (PKPD) profile and to assess its therapeutic potential as a novel therapy for hyperprolactinemia and prolactinomas.

Methods: Five non-pregnant female subjects (21-77 years), with prolactinomas (n=4) or idiopathic hyperprolactinemia (n=1) and baseline prolactin levels 39-470 ng/mL, participated in an inpatient dose-response study. Subjects received up to 3 oral doses of ropinirole (0.5, 1.0, and 2.0mg), each on a separate occasion, and frequent blood samples were collected at baseline and during the 24-hour period following drug administration. The proposed population PK/PD model features a one-compartment model with linear absorption and elimination to describe ropinirole PK, and an indirect response (IDR) model (Type I) to capture the inhibition effect of ropinirole on prolactin secretion. The time-dependent receptor desensitization was incorporated into the subjects whose prolactin concentration reached nadir before the corresponding ropinirole concentration reached Cmax. The hill factor was added to capture the sigmoidicity exhibited in the data. A conventional 2-step approach was used in conducting the fitting. First, ropinirole concentrations were fit with the population PK model. The parameters to describe ropinirole PK include CL/F, Vc/F, Ka, and Tlag. Second, the empirical Bayes estimates of ropinirole PK parameters obtained in step 1 were fixed, and the predicted individual PK profiles were used as input functions in the PD model to drive the inhibition effect on prolactin secretion. The parameters to depict the ropinirole exposure-response (Kin, Baseline, IC50, Alpha, Gamma) were fit simultaneously, where Gamma is the hill factor to characterize the sigmoidicity in the data, and Alpha is the exponential slope of receptor desensitization.

All PK parameters and most PD parameters with between-subject variability (BSV) that were estimated were assumed to be log-normally distributed. Due to the limited identifiability provided by the data, Gamma was estimated as same value across subjects, and Imax was fixed to 1. The residual variability was estimated with the additive plus proportional error model in the PK part and with the proportional error model in the PD part.

Results: The population PK model reasonably described ropinirole plasma concentrations across all three dosing levels. All population means and variance parameters in the PK model were well estimated, where the relative standard errors of the estimates were moderate (<60%). The indirect response model (Type I) was used for the description of the exposure-response relationship between ropinirole and prolactin [1]. In 3 out of 5 subjects, a time-dependent desensitization term was multiplied by the Imax term in the model to account for this backward shift of peak drug effect from peak drug concentration [2]. The ratio of %Inhibition of prolactin secretion over ropinirole AUC in the desensitization group (1.5±0.6) was lower than

that of the non-desensitization group (3.2±0.7). The sigmoidal Imax model for the inhibition of prolactin input rate (Kin) was superior to the basic Imax (>100 reduction in the objective function value, p<1.5E-23).

Conclusions: Utilizing a carefully collected high-density data set from a unique clinical cohort of hyperprolactinemic patients, this population PD model adequately describes the temporal relationship between ropinirole exposure and the inhibition of prolactin release. This model demonstrates that ropinirole significantly inhibits prolactin secretion in patients with hyperprolactinemia. Time-dependent D2 receptor desensitization was detected in 3 out of 5 subjects, indicating screening for desensitization during the initial treatment may be beneficial, as subjects with D2 receptor desensitization will need an increased dose to achieve the same degree of inhibition. Further studies investigating the long-term effect of ropinirole on prolactin levels are needed to establish ropinirole's utility as a pharmacologic alternative for the treatment of prolactinomas and hyperprolactinemia.

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IV-13: *Rasmus Jansson Löfmark* Pharmacokinetic population modelling of a GLP1 beta cell targeting oligonucleotide

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Introduction:

Targeted drug delivery to a desired cell type is an emerging science which is conceptually straightforward but mechanistically complex. Tissue targeting can largely be divided into 1) chemical modifications of the drug 2) using a targeting ligand that is linked to the cargo (i.e. conjugation) 3) adapting the drug formulation or 4) changing the physical shape of the formulation.

Tissue targeting for oligonucleotides to hepatocytes by conjugation of drugs to the tirantennary N-acetyl galactosamine (GN3) enhances the uptake into hepatocytes through internalization of the oligonucleotide by the cell-surface lectin receptor ASGR, improving apparent potency of the ASO by 10-60-fold [1,2]. Currently there are several oligonucleotides in clinical trials also demonstrating the advantage of this targeting approach for hepatocyte targets. Tissue targeting to other cell types is less well established and challenging [3]. Recent data reported by Ämmälä et al showed thatan anti-sense oligonucleotide (ASO) conjugated to an engineered GLP1 peptide resulted in a >75% knockdown of the target gene in mouse beta cells in pancreas [4,5] at low doses. These data were of particular interest since an untargeted ASO will not reach these cell types. Although these data were encouraging, little information is known about the pharmacokinetics of the ASO conjugated to a GLP1 agonist.

Objectives:

- Assess the plasma and pancreas pharmacokinetics of the GLP1-linker-ASO conjugate and its components after single dose administration to mice
- Build a population pharmacokinetic plasma-pancreas model of the GLP1-linker-ASO conjugate to further guide chemical optimization of GLP1-linker-ASO conjugates

Methods:

The in vivo study was performed in two parts. In the first part C57B6 mice (n=63) were divided up into three dose groups. Group 1 (n=15) were dosed with the GLP1 targeting ligand alone, group 2 (n=24) was dosed with the targeting conjugate and group 3 (n=24) was dosed with the ASO alone. All animals received subcutaneous administration at equimolar dosing close to the expected maximum tolerable dose of the conjugate. Based on prior knowledge the sampling time points for group 1 were 10 min, 30 min, 1, 4, and 8h. For group 2 and 3 the sampling points were 0.5 h, 1, 2, 4, 8, 24, 72, and 120 h. In the second part of the study only the targeting conjugate was dosed to C57B5 mice (n=13) but at two lower doses in order to asses nonlinearity in PK. The samplings points here for this part were 4, 8 and 24 h. All sampling were terminal readouts with three animals per time point in the first part and 2 or 3 animals per time point in the second part. At each readout plasma, kidney, liver and pancreas were collected for bioanalysis of free

targeting ligand, total targeting ligand, free ASO and the sum of ASO still connected to the linker and ASO in intact conjugate form.

Since all sampling were only terminal readouts and no individual time-profiles were generated the data were in this sense sparse. However, because a substantial number of animals were used a population modelling approach was ideal to handle this sparsity. The model considered the pharmacokinetics of GLP1-linker-ASO conjugate, its formation and clearance of the GLP1 agonist, the ASO with the linker and the unconjugated ASO both in plasma and pancreas for a total of five different observation compartments.

Results:

The model could adequately describe the pharmacokinetics of the GLP1-linker-ASO conjugate, its formation and clearance of the GLP1 agonist, the ASO with the linker and the unconjugated ASO both in plasma and pancreas. In the current studied dose range, pharmacokinetics was linear for all components in all matrixes.

The degradation rate of the intact GLP1-ASO targeting conjugate and the GLP1 agonist was rapid with a half-life of less than one hour in plasma. In pancreas, the intact GLP1-ASO targeting conjugate and the GLP1 agonist was also rapidly degraded with a half-life of less than one hour whereas the formed unconjugated ASO had a pancreas tissue half-life of approximately 70 hrs.

Conclusion:

The current presented pharmacokinetic model characterizes the pharmacokinetics of the GLP1-linker-ASO after single dose administration to mice. The model can be used as a platform to further gain insights in characteristics for a successful targeting conjugate to beta-cells and to further guide chemical optimization of GLP1-linker-ASO conjugates.

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IV-14: *Philip Lowe* Ligelizumab Paediatric Investigation Plan: exposure-response analysis in adult chronic spontaneous urticaria with simulation-based design of adolescent dose-finding

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Objectives: Ligelizumab is an investigational monoclonal antibody that binds immunoglobulin E (IgE) with higher affinity than omalizumab and has the potential to benefit a greater proportion of patients with chronic spontaneous urticaria (CSU). In establishing the paediatric investigational plan (PIP) due note was made of a significantly reduced potency, i.e. higher EC50 of omalizumab in the adolescent CSU population [1] compared with adults. It could not therefore be assumed that equivalent concentrations of ligelizumab in adolescent and adults would result in equivalent efficacy in adult and adolescent populations. The objective was to design an adequate adolescent study to determine whether the EC50 for adolescent CSU patients was sufficiently different from adults as to demand a different posology.

Methods: Ligelizumab concentrations and urticaria activity scores (UAS7, 7 day sum of daily itch and hives, each with range 0-3) were collected from adult patients treated with placebo, low, medium and high dose levels every 4 weeks multiple and a high single dose ligelizumab in a Phase 2 study [2]. Interim data from 295 patients were analysed with longitudinal pharmacokinetic-pharmacodynamic models for the continuous UAS7 (range 0-42) using NONMEM with importance sampling. The resultant model was used with stochastic simulation-estimation to design an adolescent (age 11-17 years inclusive) study with the ability to detect shifts in EC50 between adolescents and adults. A combination of R-3.2.3, NONMEM 7.3.0 [3] and PDx-Pop-5.2 software was used to create analysis datasets, estimate parameters, control the NONMEM runs and post-process results.

Results: The chosen two-compartment pharmacokinetic model described well the drug concentration data. The key exposure parameter, clearance, was 0.85 L/d (residual standard error, RSE, 9.1%) for 80 kg bodyweight with 49% coefficient of between subject variation (BSV). Bodyweight was identified as the main covariate impacting clearance with an estimate of 1.0 (power; 35% RSE). The chosen continuous UAS7 model had an EC50 of 1.1 µg/mL (38% RSE) with very large estimated BSV (1405%) and a steep Hill coefficient of 5.72 (0.75% RSE). Visual prediction checks were deemed sufficient to initiate the adolescent study design process over a number of study options. To maintain numerical stability the BSV on EC50 was reduced from that estimated to <=300%, with a sensitivity analysis included to investigate the impact. The design chosen specified three arms: placebo, low and high dose levels every 4 weeks with a treatment duration of 16 weeks and follow-up to 40 weeks. The placebo patients should cross to the high dose after 8 weeks.

Conclusions: Despite highly variable data the exposure-UAS7 response model was able to detect and describe reasonably well placebo and ligelizumab dose-related changes over time. Estimates of ligelizumab clearance and EC50 potency for reducing the signs and symptoms of urticaria were as expectated from previous clinical studies and analyses thereon [4,5,6]. Stochastic simulation-estimation indicated that a design with two active dose levels plus a placebo control should suffice for the prospective adolescent study. The low dose was prioritised as this would generate concentrations in the region of the expected EC50, the optimum point of sensitivity for estimating this parameter. The randomisation was therefore uneven, with 20 patients on the low dose, 10 patients each on the high dose and placebo. The high dose, from both the directly treated and crossed-over placebo patients, would enable estimation of the

maximum drug effect. Overall, based on 100 simulation-estimations, the procedure indicated that there was approximately 80% chance to detect a 2-fold increase in EC50, the threshold above which a different posology from adults should be considered. The pharmacometric analysis will be the subject of a separate pooled modelling and simulation study as per PIP.

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IV-15: *Qiang Lu* Population pharmacokinetic analysis of dupilumab in adult and adolescent patients with asthma

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Objectives: Dupilumab, a fully human interleukin (IL)-4 receptor α mAb, inhibits signaling of IL-4 and IL-13, key drivers of type 2 inflammation[1]. Dupilumab is approved for treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis (AD). Dupilumab has also demonstrated positive efficacy for the treatment of asthma in patients 12 years or older. This analysis aimed to (1) develop a population pharmacokinetic (Pop PK) model for dupilumab and assess the influences of intrinsic and extrinsic factors on dupilumab PK in patients with moderate-to-severe asthma; and (2) use the model to determine dupilumab exposure in severe oral corticosteroid (OCS)-dependent asthma patients who were not included in model development.

Methods: The Pop PK model was developed using concentrations of functional dupilumab in serum pooled across six phase 1, two phase 2, and one phase 3 studies in adult and adolescent patients with moderate-to-severe asthma after subcutaneous (SC) administration as well as healthy subjects after intravenous or SC administration. The base model structure from a previously developed Pop PK model in AD patients[2] was used: 2-compartment with parallel linear and nonlinear saturable Michaelis-Menten [M-M] elimination, with body weight included as a covariate on central volume (V_c). Forward selection and backward elimination were used to evaluate the following covariates: demographics, lab parameters of renal and liver function, anti-drug antibodies (ADAs), baseline biomarkers/disease characteristics (blood eosinophils, fractional exhaled nitric oxide [FeNO], % of predicted normal forced expiratory volume in one second [FEV_1%]), and population (healthy subjects vs asthma patients). The final model was validated by visual predictive checks and bootstrap. Additionally, dupilumab PK from severe OCS-dependent asthma patients were evaluated with a maximum a posteriori (MAP) Bayesian analysis using the established asthma Pop PK model.

Results: The final Pop PK model development dataset included 1,912 asthma patients (including 68 adolescent patients) and 202 healthy adults, with 14,584 concentrations of dupilumab. The PK of dupilumab in asthma patients were adequately described by a 2-compartment with parallel linear and nonlinear saturable M-M elimination model plus first-order absorption. The population estimates of the key PK parameters in asthma patients were similar to AD patients[2] and were: volume of distribution at steady-state 4.37 L, linear elimination rate 0.042 day^{-1}, and bioavailability 60.9%. As in AD patients, body weight was the primary source of variability in PK, with lower body weight associated with higher PK exposure. Compared with a typical 78 kg (median) patient, steady state area under the concentration time curve was 48.0% and 40.7% lower in a 116 kg (95^{th} percentile) patient and 43.8% and 36.1% higher in a 60 kg (typical weight of adolescents) patient, at phase 3 study doses of dupilumab 200 and 300 mg q2w (every other week), respectively. Other statistically significant covariates (ADA, albumin, and creatinine clearance) had no clinically meaningful effect, with less than 20% change in exposure estimates at 5^{th} or 95^{th} percentile of the covariate range relative to the median. All other covariates, including age (12–83 years), gender, race, laboratory parameters of liver function, biomarkers/disease characteristics (eosinophils, FeNO, and FEV_1%), and population had no statistically significant effect on dupilumab PK in asthma patients. Moreover, the concomitant use of common asthma medications has no effect on dupilumab PK, based on post-hoc analysis. Dupilumab PK in severe OCS-dependent asthma patients and non-OCS dependent

asthma patients was highly comparable; the established asthma Pop PK model was able to accurately predict dupilumab exposure in OCS-dependent asthma patients.

Conclusion: The Pop PK model adequately described dupilumab PK in adult and adolescent patients with asthma and enabled robust prediction of individual patient exposure. PK properties of dupilumab in asthma patients are comparable to those of AD patients. Only body weight exerted a noticeable effect explaining between-subject variability in the PK of dupilumab, but dose adjustment for weight is not warranted based on results from pivotal clinical studies. There is no PK difference between adolescent and adult patients after correction for body weight.

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IV-16: *Rubin Lubomirov* Population pharmacokinetic-based targeted exome sequencing (PopPK-TES) approach to assess the impact of genetic variants on pharmacokinetics of lurbinectedin in patients with advanced cancer

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Objectives: To develop a population pharmacokinetic-based targeted exome sequencing (PopPK-TES) strategy aiming to assess the impact of genetic variants on pharmacokinetics of lurbinectedin in patients with advanced cancer.

Methods: Lurbinectedin, a new RNA polymerase II inhibitor, is currently being tested in a Phase III study in patients with small cell lung cancer (SCLC), and Phase I/II studies of other solid tumors. The plasma concentrations of lurbinectedin from advanced cancer patients participating in 12 phase I and II clinical trials were pooled and fitted to a population pharmacokinetic (PopPK) model using non-liner mixed-effects modelling implemented in NONMEM v7.3 [1]. On the basis of PopPK analysis, restricted to the subset of patients who gave written informed consent for genetic testing, lurbinectedin interpatient variability on clearance (etaCL) was used as a phenotype, considering that this parameter would best reflect the remaining unexplained variance in lurbinectedin elimination that could be accounted for by genetic variations. Histogram plots and the "probit" distribution of etaCL values were used to identify the subpopulations of low and high CL outliers (i.e. patients with high and low lurbinectedin plasma exposure, respectively) as cases and controls, respectively. The germinal DNA (gDNA) was extracted from peripheral blood mononuclear cells. Targeted exome sequencing of 42 genes involved in lurbinectedin metabolism and transport was performed in an Ion PGM™ System for Next-Generation Sequencing (NGS) using an Ion 318™ chip v2 for every ten samples. The analysis of the identified variants in PGM v5.0.2 was done with Ion Reporter v5.2 software and Annotate Variants Single v5.2 workflow, specific for GRCh38_human_5.0. The associations in the case and control population were assessed by comparing allelic frequencies between cases and controls using PLINK 2.0 [2].

Results: A three-compartment mammillary model with linear distribution and elimination from central compartment was suitable to describe the time course of plasma concentrations of lurbinectedin after i.v. administration to advanced cancer patients. The model estimated a volume of distribution at steady state of 434 L that caused the distribution to deep tissues and a low central volume of 16.7 L while CL was 11.1 L/h. The model detected several covariates that affected CL: serum albumin, serum alpha1-acid-glycoprotein (AAG), body surface area (BSA), the presence of strong or moderate CYP3A4 inhibitors, and cardiac function measured by left-ventricular ejection fraction (LVEF). Histogram plots and the "probit" distribution of etaCL values of the subset of 180 patients signed written informed consent for genetic testing, allow the identification of subpopulations of low (n=10) and high (n=10) CL outliers. gDNA of these 20 patients was used to perform NGS of promoters (including 1 Kbs up-stream), all exons and 3'-UTR of 42 genes. The detected genetic variants were analyzed comparing their allelic frequencies between cases and controls. Genetic variants located in relevant genes were identified.

Conclusions: The applied PopPK-TES approach may allow discover genetic variants associated with the variability in pharmacokinetics of lurbinectedin in patients with advanced cancer. These results need further confirmation in an independent population of advanced cancer patients treated with lurbinectedin.

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IV-17: *Sreenath M Krishnan* Accuracy in the estimation of the hazard in simultaneous and sequential estimation approaches of tumor size and overall survival (OS) modeling

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Objectives: Frequently suggested tumor metrics of predicting overall survival (OS) in different tumor types are tumor-size time course (TSt), tumor size ratio at e.g. 6 weeks (TSRw6), time-to-tumor growth (TTG), and the tumor growth rate constant (KG) [1,2]. In addition to the accuracy of tumor metrics, the estimation approach used for connecting tumor metrics to OS might also influence the estimated hazard (HZ) of death, in a similar way as when models of PK are connected to PD models [3]. For example, Empirical Bayes estimates of tumor metrics may be shrunk and thereby affect the estimated OS parameters [4]. Moreover, a tumor size – OS model could ideally be applied early in a treatment to predict the adequacy of the dosing regimen for an individual patient. This study aims to investigate how sequential and simultaneous estimation approaches, as well as the number of tumor size measurements, influence the accuracy of estimated HZ of death for an individual patient.

Methods: ***Data***: Tumor size data for 1000 subjects were simulated using a simplified tumor growth inhibition model for bevacizumab plus chemotherapy in colorectal cancer[5], at baseline(w0), and at 6,12,18,24,36,48,60,72,84 and 96 weeks. Dropout from tumor measurements was considered and forced at an observed increase from the tumor nadir of >20%. The OS data were simulated using a Weibull function and tumor metrics [5]. The accuracy of the estimated HZ was calculated as the percentage deviation from the 'true' HZ and the acceptable accuracy was set to 80-125% of the 'true' HZ. ***Sequential approach*****:** *(a)* The Empirical Bayes estimates were derived from the simulated individual profiles and the prospective evaluation function in PsN[6]. The individuals' tumor model parameters were applied in the derivation of tumor metrics and the estimation of HZ, similar to 'Individual PK Parameters (IPP)' approach. *(b)* Alternatively, the tumor data and the population tumor parameters were used in the derivation of the tumor metrics and the estimation of the HZ, similar to 'Population Pharmacokinetic (PK) Parameters and Data (PPP&D)' approach. ***Simultaneous (SIM) approach*****:** Tumor parameters and OS parameters were estimated simultaneously using a joint model. In all scenarios, the influence of the number of tumor size observations in the estimation of HZ was investigated.

Results: ***TSRw6:*** When w0 and w6 measurements were used, 69% (IPP) and 70% (PPP&D and SIM) of individuals had an acceptable accuracy. By adding w12 measurements, the corresponding percentages were 78% (IPP) and 79% (PPP&D and SIM). The accuracy was little influenced by later observations and accuracy percentages were 81% (IPP) 84% (PPP&D) and 87% (SIM) when all tumor data was used. ***KG*****:** When tumor data until w6 used, the percentage of the population with acceptable accuracy was 54% (IPP) and 55% (PPP&D and SIM). The accuracy was little affected by adding w12-w24 measurements, while adding tumor data beyond w24 increased the accuracy (median TTG was 23 weeks) and it was 62% (IPP and SIM) and 63% (PPP&D) when all tumor data was used. ***TTG*****:** The percentage of population with accurate HZ was always lower than 45% for all estimation approaches despite of including more tumor data. With data until w6, the accuracy was 23% (IPP) and 26% (PPP&D and SIM). The accuracy was highest at w36; 36% in IPP, 40% in PPP&D and 43% in SIM. ***TSt*****:** The accuracy increased with longer tumor follow up. With data up to w6, 39% (IPP and SIM) and 41% (PPP&D When all tumor data was used, the percentages of remaining patients at w96 were 44% (IPP), 46% (PPP&D) and 41% (SIM).

Conclusions: This simulation study demonstrated comparable results between sequential and simultaneous approaches in investigating tumor metrics as predictor of OS. In the scenarios investigated here, the PPP&D approach would be preferable since it had shorter runtimes compared SIM and slightly better results than IPP. The analysis method had little influence on the accuracy of the estimated HZ, while the accuracy in the estimated individual HZ was dependent on which metric that was defined as the true one. When TSRw6 was the predictor, fewer measurements were needed to predict its value [7] and the HZ accuracy was here found to be relatively high already at w12-w18, while longer follow up was needed to improve the accuracy for KG, TTG & TSt metrics and estimated HZ.

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IV-18: *Lei Ma* Efpeglenatide dose selection for a phase 3 study in type 2 diabetes mellitus (T2DM) patients: pharmacokinetics and pharmacodynamics (PK/PD) modeling, network meta-analysis and clinical trial simulation

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Sanofi

Objectives:

Efpeglenatide (efpeg) is a glucagon like peptide -1 receptor agonist (GLP-1 RA) being developed for the treatment of type 2 diabetes mellitus (T2DM). The primary objectives of this analysis were to: assess efficacy of different efpeg doses based on an established longitudinal exposure-response (E-R) model between efpeg and changes in glycated hemoglobin A1c (HbA1c) with selected covariates; compare with competing GLP-1 RAs and perform clinical trial simulations (CTS) to evaluate the probability of success (POS) of a head-to-head trial and guide efpeg dose selection and comparator selection for the trial.

Methods:

Efpeg pharmacokinetic (PK) and efficacy (HbA1c) data were obtained from 5 clinical studies (1 Phase 1b and 4 Phase 2) in T2DM and obesity populations with treatment duration ranging from 8 to 22 weeks. A sequential population PK/PD model for HbA1c was developed using nonlinear mixed effects modeling program, NONMEM (version 7.3). Relevant covariates, such as baseline HbA1c, body weight, age, sex, race and obesity were also evaluated. Based on the established E-R model, stochastic simulations were performed to illustrate the impact of various efpeg dosing regimens on the change from baseline HbA1c (%) difference from placebo in subjects with T2DM and obesity. Network meta-analysis was used to synthesize competitive intelligence while CTS were used to evaluate the POS of phase 3 head-to-head study by leveraging meta-analysis results.

Results:

The indirect response model incorporating an exponential plateau non-drug effect adequately characterized the longitudinal HbA1c data in subjects with T2DM or non-diabetic overweight to obese subjects. The final HbA1c E-R model included the following statistically significant covariates: baseline HbA1c on maximum decrease in log HbA1c due to treatment effects (I_{max}), first-order rate constant describing the temporal delay between drug concentration and subsequent changes in HbA1c (k_{out}) and maximum placebo effect; female sex on I_{max}; and obese subjects on k_{out}. The efpeg concentration that results in 50% of the maximal drug effect (IC_{50}) was estimated to be 165 ng/mL. For example, the average predicted efpeg concentration (C_{avg}) for a 4 mg once a week (qw) dosing regimen at steady-state in T2DM patients is 581 ng/mL. At this concentration, 78% of the maximal percentage reduction in HbA1c is achieved.

CTS were performed using the final PK/PD model to evaluate the POS of efpeg treatments against potential comparators. The head to head trial includes four arms (n = 300/arm) with one placebo arm, two efpeg arms (4 mg and 6 mg, qw) and one comparator arm Dulaglutide (dula) 1.5 mg or Semaglutide (sema) 1 mg (both qw). The treatment duration is 30 week. The dropout rate is assumed to be 15% and 10% for placebo and efpeg groups, respectively. Treatment effects for comparators on HbA1c were based on AWARD trials 1, 5 and 6[1-3], SUSTAIN trials 1, 3, 6 and 7[4-7], LEAD 2[8] and DURATION 1[9]. A network model was used to

leverage information from multiple clinical trials to increase precision of the estimated effects of competitors and reduce the biases. The comparison between efpeg and sema is estimated through two routes: 1) efpeg→placebo→sema and 2) efpeg→lira→placebo→sema. Liraglutide (lira) data have two contributions to the analysis: 1) help to benchmark lira effect for comparison between lira and efpeg and 2) placebo arm helps to estimate placebo effect more precisely. CTS suggested that:

- 6 mg efpeg has high chances to be superior to dula on HbA1c (POS = 88%)
- 6 mg efpeg has comparable performance to sema on HbA1c (POS = 76% to show non-inferiority).
- 4 mg efpeg has high chances to be non-inferior to dula on HbA1c (POS = 99%)

Conclusions:

- The indirect response model incorporating an exponential plateau non-drug effect adequately characterized the longitudinal HbA1c data in subjects with T2DM or non-diabetic overweight/obese subjects.
- The magnitude of the non-drug effect was dependent on the baseline HbA1c value such that a larger maximum decrease in HbA1c was predicted for subjects with higher baseline HbA1c.
- Upon repeated dosing, the large majority of the maximum effect on HbA1c attributed to efpeg exposure was predicted to be obtained by approximately 12 weeks.
- Based on CTS, 6 mg/qw efpeg would have high POS to demonstrate superiority against dula (88%) and non-inferiority against sema (76%) on HbA1c in a head-to-head trial.

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IV-19: *Matthias Machacek* A Systems Pharmacology model of peripheral serotonin production proposing two different synthesis compartments with markedly different release rates into blood

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Objectives: High levels of systemic serotonin (5-HT) are implicated in several diseases including carcinoid syndrome, pulmonary arterial hypertension and obesity. Systemic 5-HT is produced from dietary tryptophan (Trp) where the rate limiting step its catalysis by tryptophan hydroxylase 1 (TPH1). A TPH1 enzyme inhibitor was recently approved for treatment of carcinoid syndrome and others are in development. To enable observation of changes in 5-HT synthesis in vivo on an hour time scale and to test new TPH1 inhibitors we previously described an approach utilizing a stable isotope Trp tracer (h-Trp) [1]. The aim of the current study was to develop a Systems Pharmacology model to explain the kinetics, distribution and compartmentalization involved in h-5-HT and 5-HT production and to utilize the model to predict from single dose experiments long term effects on 5-HT with chronic dosing of TPH1 inhibitors.

Methods: Data from a h-Trp study in Beagle dog was used to develop a pharmacokinetic (PK)/ pharmacodynamic (PD) model. Dogs received a single oral dose of 12 mg/kg h-Trp one hour after receiving orally vehicle, 0.2, 1 or 5 mg/kg of a TPH1 inhibitor. TPH1 inhibitor PK, h-Trp, Trp, h-5-HT and 5-HT observations were available for 1 day, and 5-HT pathway observations in the vehicle group for 11 days. As expected for a single dose treatment, no effect on whole blood 5-HT was observed due to its slow turnover. A compartmental population PK/PD approach was used to describe the concentration-time curves of the enzyme inhibitor in plasma, and h-Trp, Trp, h-5-HT and 5-HT in whole blood. It was assumed that the distribution parameters were identical for the isotope labeled and non-labeled species. Further, the enzymatic reaction rates were assumed to be identical and the competition between Trp and h-Trp for the enzyme TPH1 was modelled as described in [2]. The simples t compartment structure was sought that would explain the observed data and the model parameters were estimated with Monolix 4.3.3.

Results: Trp had a three-compartmental kinetics with the first two distribution half-lives of 6.5 minutes and 7.6 hours, and a terminal half-life of 5.8 days. The conversion of Trp to 5-HT occurred in two different peripheral effect compartments with two very different exchange rate constants for 5-HT with the plasma compartment. These two reaction compartments were different from the two peripheral compartments for the distribution of Trp and simpler models were unable to describe the observed h-Trp and h-5-HT. In the first compartment, h-5-HT had a half-life equivalent of 6.7 seconds and in the second compartment of 16.9 hours. Thus, after oral intake of h-Trp there was immediate appearance of h-5-HT in the circulation because of the fast compartment; while the slow compartment was responsible for the storage and release of h-5-HT into the circulation after h-Trp has been eliminated. The half-life of whole blood 5-HT in dog was estimated as 4.2 days. Plate lets, that are the main site of 5-HT storage in blood have a half-life of 3.3 days [3]. From the model, it was found that 90% of the 5-HT is in blood, 10 % in the slow storage compartment and 0.001% in the fast storage compartment. For model validation, the effect of daily dosing of 30 mg/kg of the TPH1 test inhibitor administration for 2 weeks on whole blood 5-HT in dogs was successfully predicted. Further, the model correctly predicted the blood Trp levels in dog after 24 hours fasting followed by daily feeding for 11 days.

Conclusions: The model built from the stable isotope tracing data indicated the need for slow and fast 5-HT production compartments. The fast release compartment is likely the gut, the major site of peripheral 5-HT synthesis. The second compartment may represent synthesis in other organs such as lung [4] or a slower release process from gut at a different time scale. 90% of the 5-HT is stored in platelets and only 10% at the site where it is synthesized. Different sites of peripheral 5-HT synthesis and different exchange rates will be critically relevant to the design and development of novel effective TPH1 inhibitors. Further, the System Pharmacology model can be further developed as a translational tool to predict doses of TPH1 inhibitors to reach different 5-HT lowering thresholds in patients.

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IV-20: *Paolo Magni* Evaluation of software tools for Bayesian estimation on population models: an update based on current software versions

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Objectives: Bayesian modelling based on Markov Chain Monte Carlo (MCMC) methods is acknowledged as a useful instrument in pharmacometrics. This work provides, 3 years after, an updated picture of a previous study [1], in which the performances of several software tools performing Bayesian estimation in a population context were compared in terms of efficiency and reliability of estimates, using as case studies an algebraic model and an ordinary differential equation (ODE) model.

Methods: NONMEM 7.4.1, WinBUGS 1.4.3 (with BlackBox Component Builder 1.5 and WBDiff interface), Stan 2.17, and JAGS 4.3 (with R packages Rstan and RJags) were selected for the present evaluation. In NONMEM, both BAYES and the newly added NUTS methods were evaluated, with and without mu referencing model implementation. The first model selected as a case study was a Poisson count model, describing a clinical trial of an anticonvulsant therapy. Data of seizure attacks, covariates and priors were collected from a published study [2]. The second model was a two-compartment PK ODE model [3] for a Phase I study of a monoclonal antibody for epilepsy. Simulated data were generated via Simulx, and priors were defined based on literature data [4]. For each model and tool, the number of iterations in the burn-in and stationary phases was computed based on the Raftery algorithm [5] (raftery.diag function in R coda package), to obtain a number of independent samples able to describe the posterior distribution with sufficient precision. Posterior distributions were inspected and compared. The capability of the tools to obtain uncorrelated samples was evaluated through the K parameter, i.e. the number of consecutive samples of the generated Markov chain that have to be discharged to obtain a new chain of “independent” samples. The Effective Sample Size per execution time unit (ESS/T) was calculated as an efficiency index. The study was conducted on a Windows 10 ASUS desktop PC, with Intel Core i5 3.30Ghz 4 cores and 8GB RAM.

Results: For the count model, the posterior distributions of all the tools were similar to the expected ones [2]. In terms of execution times, Stan was the fastest (28 s), followed by NONMEM NUTS and BAYES methods with mu referencing (33 and 38 s), and WinBUGS and JAGS (~100 s). Estimation in NONMEM without mu referencing requested more than 4 min. The NUTS method, implemented both in NONMEM and Stan, showed the lowest K values, demonstrating its capability to generate almost independent samples. As for ESS/T, NONMEM NUTS and BAYES methods with mu referencing showed better performance with respect to the other tools; compared to BAYES, NUTS slightly improved both the efficiency and the estimation results.
For the ODE model, all the tools completed the estimation process, except for NONMEM NUTS method without mu referencing (due to convergence issues), and JAGS (it does not include an ODE solver). No tool was able to recover the expected posterior distributions [4] for all model parameters: variances of residual variability terms were always over/under-estimated. NONMEM BAYES and NUTS methods with mu referencing provided the most reliable results, whereas Stan estimated biased and highly skewed posterior distributions. The lowest execution times were obtained with NONMEM NUTS and BAYES methods with mu referencing (8 and 10 min), followed by WinBUGS (19 min), Stan (63 min), and NONMEM BAYES method without mu referencing (4.8 h). Again, the NUTS method displayed the lowest K values, followed by

NONMEM BAYES method with mu referencing, WinBUGS, and NONMEM BAYES method without mu referencing. In terms of ESS/T, the best performances were obtained with NONMEM NUTS and BAYES methods with mu referencing for fixed effects, whereas WinBUGS showed higher ESS/T for random effects. NONMEM BAYES method without mu referencing and Stan showed always considerably lower ESS/T.

Conclusions: Based on the tested count and ODE models, according to the computed posterior distributions and ESS/T, NONMEM with mu referencing (in particular with the NUTS method) appears to be the best choice for reliable and efficient Bayesian estimation. It is followed by WinBUGS (or equivalently JAGS but for algebraic models only), which still represents a more flexible choice for Bayesian analysis compared to NONMEM (despite the significant advances of its version 7.4). Finally, note that significant improvements were made for ODE models Bayesian estimation in the latest release of Stan, even if estimates are not as satisfactory as for other tools.

Acknowledgments: The authors thank Dr. Robert Bauer for his technical support on NONMEM.

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IV-21: *Corinna Maier* Improving model-based predictions of neutropenia using sequential data assimilation

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Objectives:

One of the major side effects of cytotoxic anticancer treatment is neutropenia, a severe reduction of neutrophils that puts patients at high risk of life-threatening infections. Reliable predictions of chemotherapy-induced neutropenia can help to early identify patients at risk as well as patients at subtherapeutic doses. Predicting the neutrophil time course can also support individualised dosing schedules. Novel measurement devices in digital health care, allowing for frequent neutrophil monitoring at home, require the application of new recursive data processing methods that enable decision support in ongoing treatment. Recursive data processing is well established in the field of meteorology in the form of sequential data assimilation (DA) methods that are used to improve model-based weather forecasts as new data becomes available. The objective of this study was to investigate the application of sequential DA techniques in the field of systems pharmacology. Based on the example of neutropenia, induced by the cytotoxic anticancer drugs docetaxel or paclitaxel, the benefits of sequential DA methods should be examined.

Methods:

In contrast to batch processing of data, sequential DA methods provide a framework to recursively process data [1]. This results in iterative cycles of forecasts based on mathematical models and combining these computer-generated forecasts with measurement data in real time. In these cycles the posterior is recursively updated based on Bayes' formula. For applications in systems pharmacology, particle filter algorithms are particularly suitable, as they are sequential DA methods that allow for non-Gaussian error models and nonlinear structural models. The particle filter distribution approximates the current posterior distribution, which integrates all prior information up to the current data point.

For the simulation study, we used prior knowledge from a population analysis [2] of a clinical study for initialising the particle filter. The forecast was generated using the gold-standard model for neutropenia [3], for the update patient-specific data was simulated and the updated posterior functioned as prior for the next update step. For the same setting a maximum a-posteriori (MAP) estimation was performed in prior work [5], which allows for comparison of results. MAP estimation, the current state-of-the-art in systems pharmacology, provides access to the mode of the posterior distribution and is, in its basic form, non-recursive. To account for long-term effects over several treatment cycles, we used an extended neutropenia model [4] that describes bone marrow exhaustion for the anticancer drug paclitaxel.

Results:

Based on the mean of the posterior distribution as point estimate for the particle filter, both approaches have comparable root mean squared errors (RMSEs) in the parameter estimates and in the summary statistics, e.g. time to recovery or grade of neutropenia. In contrast to MAP estimation, the particle filter

also quantifies the uncertainty of these statistics by estimating the full posterior. This leads to much more informative results as the probabilities for all possible outcomes are provided and not only the most likely one. Additionally, in this recursive framework, only the current data point is needed for the update step as all prior information is already included in the previous posterior distribution. The complexity of the optimization problem in the MAP estimation, however, increases with the number of measurements. This makes the particle filter much more efficient for multiple cycle therapy and suitable for real-time implementation, which allows to support decision-makers in ongoing treatment.

Conclusions:

Using neutropenia as example, we demonstrated that sequential DA methods provide an efficient framework to recursively process patient data. With the development of novel digital healthcare devices this is becoming more and more important in systems pharmacology. In particular, we showed that the particle filter enables patient-specific predictions about the time-course of neutrophil counts, which help to identify patients at risk for super- or subtherapeutic doses and support adaptations for subsequent treatment cycles. The comprehensive uncertainty quantification, sequential data processing and easy-to-interpret results are crucial for rational and individual decision-making in oncology.

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IV-22: *Victor Mangas-Sanjuan* Defining level A IVIVC dissolution specifications based on individual in vitro dissolution profiles

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Objectives: The purpose of this work is to compare the classical approach (the use of mean data) with a new methodology in which we have used individual data in order to assess the probability of declaring bioequivalence for a new batch based on an IVIVC. Furthermore, we have evaluated the impact of these two different methodologies on the establishment of dissolution specifications.

Methods: A slow, medium and fast dissolving drug formulations were used to develop the IVIVC. Dissolution data sets were generated for 12 units (e.g. tablets) based on a first-order dissolution model and forced to show a similarity factor (f2) below 50 between the medium and fast/slow formulation. A level A IVIVC using differential equations[1] was established using these three drug formulations, where the link between in vitro and in vivo performance of the drug products was related between in vitro and in vivo dissolution rate coefficients (kd). Plasma profiles were generated using a one compartment model with first order dissolution, absorption, and elimination kinetics. Twelve individual units were considered for each formulation or batch. Batch suitability was assessed using six additional batches (12 units each). For each batch, simulation (n=1,000) of a dissolution assay with 12 units was generated through Monte Carlo simulation approach. The percentage of BE batches was computed for each approach. BE of a new batch was concluded when the Cmax ratio between reference and new batch formulations was within ±20%. Dissolution specifications were established as follows: (i) classical approach, in vitro dissolution limits of each formulation were computed using the batch whose ratio was the closest to ±20%; (ii) individual approach, the STSF and FTFF whose ratio was exactly ±20%. The simulations were performed in NONMEM 7.3[2]. Graphical and statistical analysis were performed using R software and RStudio®.

Results: According to the results from the classical approach, the Cmax ratio from the six batches fulfill the ±20% range under linear level A IVIVC. Similar results were observed for Batches 2-6 when non-linear level A IVIVC was developed, but only 78.6% of the simulations with Batch 1 achieved a Cmax ratio within the ±20% difference. However, when the individual approach was applied under linear level A IVIVC, a significant amount of simulations with Batches 1 and 2 were out of ±20% limits: 53.3 and 58.1%, respectively. Greater differences between classical and individual approaches were observed for the non-linear relationship (scenarios 4-6), where the suitable number of batches of Batch 1 and 2 diminished to 0.3 and 15.5%, respectively. Additionally, 23.1% of the simulations with Batch 3 resulted in a Cmax ratio greater than ±20% compared to the reference formulation. The dissolution performance of Batch 3 was more similar to the reference formulation than Batches 1 and 2, but differences were not detected when the classical approach was applied. The batches that were closest to ±20% difference on Cmax (Batches 1 and 2) were used to establish the dissolution limit specifications (Table 4). The classical approach provides narrower specification limits because it is established based on the mean in vitro dissolution profile that is closest to ±20%, whereas the individual approach provides the dissolution specification limits that exactly achieved ±20% difference on Cmax between reference and new batch.

Conclusions: An individual approach has been proposed to establish the dissolution specifications using a level A IVIVC, ensuring BE of all units within the new batch developed. This methodology takes into

consideration the in vitro and in vivo variability observed, providing the dissolution specification limits that ensure in vivo ratios exactly to 80-125. Thus, the widening of dissolution specification is a consequence of using individual data, but ensures the BE of all tablets, which is not always achieved using the classical approach.

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IV-23: *Jialin Mao* PBPK modelling of drug-drug interactions driven by moderate CYP3A inducers

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Objectives: In the field of in vitro –to-in vivo (IVIVE) translation of CYP3A induction, there is increasing understanding of how a PBPK approach helps to predict the magnitude of drug-drug interactions (DDI) caused by strong CYP3A inducers such as rifampicin [1]. In drug development, many drug candidates are identified as weak-moderate inducers on the basis of in vitro data. Although there are reports using a static model to predict the CYP3A driven DDI magnitude[2], the translation of in vitro data to in vivo using a PBPK approach is not well established. Therefore, there is a need for the systematic investigation beyond strong inducers or inhibitors. This work focuses on how the magnitude of DDI caused by the moderate CYP3A inducers can be predicted using a PBPK approach.

Methods: Three CYP3A moderate inducers armodafinil, pleconaril and modafinil were selected for this investigation. **In Vitro:** A range of incubation concentrations was tested in plated human hepatoctyes for 3 and 5 days, including the positive control rifampicin. The concentration of each inducer was measured at the end of the in vitro study, and incorporated in generating the EC50 and Emax based on both mRNA and activity measurement. **PBPK:** The PBPK model was constructed in Simcyp® version 15 using a mixed "bottom-up" and "top-down" approach for each inducer. The predicted PK profile was verified using clinical PK data. The in vitro Emax and EC50 were then incorporated into the models to predict the reported clinical DDI related to armodafinil, pleconaril and modafinil, specifically between CYP3A substrate midazolam (IV and PO) and armodafinil, midazolam (IV and PO) and pleconaril, and CYP3A substrate triazolam (PO) and modafinil.

Results: The constructed PBPK models were able to predict the PK profile of armodafinil, pleconaril and modafinil at the dose where the clinical DDI studies were conducted. For the induction-based DDI prediction, it is observed that the predicted magnitudes of DDI were closer to the clinical observations for all three drugs and related studies when 1) the measured inducer concentrations were used to generate the in vitro Emax and EC50 data (considering the loss of the inducer during the incubation time) and 2) the activity/mRNA data were expressed relative to the rifampicin data (calibration with the positive control). The Emax/EC50 generated with 3-day treatment provides better prediction compared those generated with 5-day treatment. In addition, the activity data demonstrated a better IVIVE than the mRNA data.

Conclusion: The current work demonstrated an approach that successfully predicted the magnitude of DDI caused by moderate CYP3A inducers. It also demonstrates the utility of PBPK modelling to provide recommendation on possible in vitro study designs. It also provided some insights to in vitro study design, including duration of hepatocyte treatment, monitoring of concentration loss and use of positive control, which could increase confidence in the DDI prediction using PBPK approach.

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IV-24: *Anita Mathias* Joint population pharmacokinetic modelling of sofosbuvir and its metabolites (GS-566500, GS-331007) in Hepatitis C Virus (HCV)-infected adolescents receiving sofosbuvir or ledipasvir/sofosbuvir

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Objectives: A joint semi-mechanistic population pharmacokinetic (PopPK) model of sofosbuvir (SOF) and its metabolites (GS-566500 and GS-331007) was developed, using pooled data across studies evaluating the safety and efficacy of sofosbuvir (SOF: Sovaldi®) and ledipasvir/sofosbuvir (LDV/SOF: Harvoni®) in HCV-infected adolescent subjects (12

Methods: Data from two Phase 2 studies in HCV-infected adolescent subjects were used for this analysis including 129 subjects with measurable plasma concentration data (40 subjects with 733 samples from the SOF study and 89 subjects with 1211 samples from the LDV/SOF study). A non-linear mixed-effects modelling approach with the first-order conditional estimation + interaction (FOCEI) method in NONMEM 7, version 7.4 (ICON, Maryland) was utilized. The impact of covariates, including age, body weight, sex, creatinine clearance (calculated CLCRSW), ribavirin (RBV) or ledipasvir (LDV) usage on the PK of SOF and GS-331007 was investigated. Based on the number of SOF samples below the limit of quantitation, the censored-data likelihood (M3) method was evaluated. Inter-individual variability was tested on central and peripheral clearance (CL/F and Q/F), central and peripheral volume (Vc/F and Vp/F), and absorption rate constant (Ka). Various models were tested to characterise the absorption profile.

Results: Plasma PK of SOF and its metabolites was described by a joint 1-compartment model with sequential first-zero order absorption for SOF, a 1-compartment model with first order absorption for GS-566500, and a 2-compartment model with first order absorption and lag time (Tlag) for GS-331007. The models were parameterized using CL/F, Q/F, Vc/F, Vp/F, Ka, Tlag, and relative absorbed fraction of each analyte (F). The orally administered SOF dose was divided into a fraction F1 leading to the parent and fractions F2 and F3 leading to GS-566500 and GS-331007, respectively, prior to reaching the circulation (accounting for the pre-systemic conversion of SOF to its metabolites in enterocytes via mucosal Cathepsin A). The sequential systemic conversion of SOF to its metabolites was also incorporated ($CL_{SOF} \rightarrow CL_{GS-566500} \rightarrow CL_{GS-331007}$) to account for the Cathepsin A and Carboxylesterase 1 mediated SOF metabolism in hepatocytes. The typical estimated CL/F values were 122.7L/hr, 86.5L/hr, and 13.7L/hr for SOF, GS-566500, and GS-331007, respectively. The relative molar% of dose absorbed was 33.6% for SOF, 11.9% for GS-566500 and 54.5% for GS-331007 respectively in the SOF study and 57.3% for SOF, 7.6% for GS-566500 and 35.1% for GS-331007 in the LDV/SOF study. Statistically significant parameter-covariate relationships identified included LDV co-administration on SOF F1, and RBV co-administration, CLCRSW, and body weight on GS-331007 CL/F.

When administered with LDV (a P-gp inhibitor), relative bioavailability (F1) of SOF (a P-gp substrate) was increased by 70%. Of the covariates examined, co-administration of RBV increased GS-331007 CL/F by 62%. GS-331007 CL/F was increased by 33% and 9% between the 5^{th} and 95^{th} percentiles of CLCRSW (106-202mL/min) and body weight (45-91kg) values, respectively, suggesting minimal clinical impact of these covariates on GS-331007 PK. Finally, both the joint population PK model and the previously developed separate models for individual analytes performed similarly as evaluated based on model diagnostics, bootstrap output and predicted post-hoc exposures (AUC_{tau} and C_{max}). Similar analysis was performed for adult population, resulting in comparable exposures.

Conclusions: SOF, GS-566500, and GS-331007 PK in adolescent HCV-infected subjects can be comparably described by joint or individual population PK models, based on model performance and post hoc exposure estimates. This analysis illustrates that a joint parent-metabolite model can provide semi-mechanistic understanding, whereas if post hoc exposure estimates are the purpose of the modeling effort, individual models are appropriate for the analysis.

IV-25: *Tomomi Matsuura* Clinical validation of a quantitative systems pharmacology (QSP) model for nerve-growth-factor (NGF) therapies

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Objectives: Despite a marked increase in the application of quantitative systems pharmacology (QSP), its role in drug development and regulatory decision making has not yet been well established. Case studies presented to date have often been retrospective in nature and may not be considered compelling enough by decision makers and regulators to significantly increase their confidence in the approach. On the other hand, due to fact that QSP is often applied in early stages of research [1], prospective predictions may never reach the point of clinical validation due to high attrition rates. Therefore, there is an urgent need for sharing case studies of clinical validation of prospective QSP model predictions [2].

Methods: Previously, we developed a QSP model of the nerve growth factor (NGF) pathway to guide selection and validation of novel targets for the treatment of pain [3]. A key, non-intuitive prediction from the model was that the concentrations to achieve clinically-meaningful analgesic efficacy for a small-molecule inhibitor of the tropomyosin receptor kinase A (TrkA) are very high (i.e. ~100-fold the *in vitro* potency). Clinical results in a battery of human evoked pain models for the first "peripherally-restricted pan-Trk inhibitor", PF-06273340, were very recently published [4] and we analysed the pharmacokinetic-pharmacodynamic (PKPD) results and compared this with our previous QSP predictions. PKPD data were extracted from the publication [4] with WebPlotDigitizer and analysed using the semi-compartmental modelling approach proposed by Kowalski and Karim [5], implemented in Phoenix version 7.

Results: PF-06273340 only met the decision rule on one of the five primary endpoints (UVB skin thermal pain detection threshold) at the highest dose tested (400 mg). Graphical exploration of the PKPD relationship showed marked hysteresis. An apparently linear effect-site concentration-effect relationship was obtained using a semi-compartmental model [5]. Through extrapolation of the model, we estimated the efficacious concentration required to mirror the effect observed with reference treatment (600 mg ibuprofen) to be 795ng/ml, which is ~275-fold and ~20-fold the primary pharmacology IC_{50} based on total and unbound plasma concentration, respectively. Assuming that these are estimates of the lower end of the concentration-effect relationship and that higher multiples are required to match the clinical efficacy of NGF monoclonal antibodies, we conclude that the data are consistent with the prospective QSP model predictions for a selective TrkA inhibitor [3], also because some of efficacy observed with PF-06273340 may be related to its TrkB activity [4]. This potential gain in efficacy would however be offset by a smaller therapeutic window over TrkB-mediated side effects in the central nervous system [6]

Conclusions: This analysis provides clinical validation of our QSP model for NGF therapies in pain. Given the very high predicted multiples of IC_{50} required to produce efficacy better than standard of care, we propose that it may not be possible to develop a peripherally-restricted small-molecule TrkA inhibitor with an acceptable therapeutic index for the treatment of pain. The quantitative guidance provided by the QSP model for the first-in-human study design is in line with new regulatory expectations with regards to calculation of starting dose and subsequent dose escalations [7]. Due to the modular nature of the model, it can be updated and extended when new biological insights become available [8] and to date we have applied it to 5 programs of different compounds/mechanisms. A mathematically reduced version of the full model has also been developed, which is more amenable for pharmacometric applications in clinical development [9].

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IV-26: *Hannah Mayer* A novel approach to estimate ontogenies for PBPK applications – From literature data to simulations

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Objectives: Application of physiologically based pharmacokinetic (PBPK) modelling in pediatric and geriatric populations requires a detailed understanding of age-dependent physiological processes (ontogenies). Important examples include the expression of certain proteins (e.g. plasma proteins, metabolic enzymes or transporters) or functional measures (e.g. glomerular filtration rate). The aim of this study was to develop a novel approach informed by ontogenetic information from literature that allows (1) to cover the complete age range (including maturation and ageing) with one generic ontogeny function and (2) to integrate individual and aggregated (e.g. mean and standard deviation) data. Resulting ontogenies will be populated in PK-Sim® as part of the Open Systems Pharmacology (OSP) suite [1].

Methods: Markov Chain Monte Carlo (MCMC) methods, which allow the usage of aggregated data in combination with individual data, are used to estimate the parameters of a function describing the typical course of the ontogeny as well as the variability around it. The typical course of the ontogeny is described using a piecewise defined function in combination with a flexible estimation of the transition points between the different pieces. The pieces are connected in such a way that the function is continuously differentiable at each point. As default there are three parts: The first one describes an increase during the maturation phase similar to a Hill function, the second one refers to a constant level in (healthy) adults and the third one describes a decrease during ageing similar to a Hill function. The variability may be modelled in an age-dependent manner making use of the continuously differentiable function. Based on the results of the MCMC the relevant quantities can be simulated in future applications taking into account the age of the simulated individual as well as variability and uncertainty for this particular age. As a first feasibility assessment the approach was applied to learn ontogenies for alpha-acid glycoprotein (AAG), Human Serum Albumin (HSA) and Hematocrit (HCT). In cases of differences with respect to gender or ethnicity separate ontogenies are fitted for each subgroup.

Results: A general applicability of the proposed approach with its flexible properties was demonstrated. Goodness of fit plots revealed that the obtained results for AAG, HSA and HCT ontogeny are in good agreement with the data. For example, the following properties shown in the data could be well described: there is no age-dependent decline for AAG, HSA levels in men are elevated compared to those in women and the decline of HCT levels in elderly is more pronounced for men than for women. The ontogenies for the plasma proteins HSA and AAG were qualified by a comparison of measured and predicted fraction unbound values in children and adults.

Conclusions: The newly developed approach can adequately describe ontogenies over the complete age range and reflects the observed variability. It comprises a hill-function-like increase during the maturation phase and a hill-function-like decrease during the ageing phase. This approach could be applied to derive ontogenies for PBPK applications in pediatric and geriatric populations.

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IV-27: *Christophe Meille* PKPD modeling of preclinical anti-tumor activity translates to first-in-human phase I study of MDM2 inhibitor HDM201

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Objectives: The purpose of this work was to investigate the predictability from preclinical to clinical of a model-based analysis capturing drug action on tumor size kinetics, and its application in the clinical development of HDM201 for exposure-efficacy relationships, optimization of dose regimen selection, and predicting clinical outcomes.

Methods: Plasma concentrations, and tumor size data were collected from preclinical SJSA-1 (a wild-type p53 and MDM2-amplified osteosarcoma cell line known to be sensitive to MDM2 inhibition and p53 reactivation) tumor bearing rats and from the ongoing Phase I study of HDM201 in patients with TP53 wild-type solid tumors [1]. Population PKPD modeling was used to investigate the pharmacokinetics of HDM201 linked to the time-course of the anti-tumor effect in both the SJSA-1 xenograft rat, as well as in clinic as a function of dose and treatment schedule. In patients, tumor size assessments were conducted, with longitudinal sum of largest diameter (SLD) change post-dose relative to baseline. This data was obtained from the on-going first-in-human CHDM201X2101 trial. This dataset included 85 patients randomized to receive NVP-HDM201 every 3 weeks (Q3W; *n* = 26; 12.5 to 350 mg), QW (D1, D8 of a 4-wk cycle; *n* = 20; 120 to 200 mg), QD for 14 consecutive days (4-wk cycle; *n* = 20; 1 to 20 mg), and QD for 7 consecutive days (4-wk cycle; *n* = 19; 15 to 25 mg). Firstly, preclinical tumor growth inhibition (TGI) modeling was applied to understand scheduling requirements for antitumor activity in clinic, and secondly, TGI modeling was applied on clinical data to validate the translational PKPD modeling approach [2].

Results: The PKPD relationship among HDM201 exposure and TGI in the preclinical SJSA-1 xenograft model was well characterized. A signal distribution model with a saturating growth best described the time-course of longitudinal tumor growth as a function of dose and treatment schedule [3]. Incorporation of a resistance component was necessary to characterize tumor regrowth in the presence of HDM201 across multiple treatment cycles. The results from preclinical PKPD modeling did not identify a schedule dependency with tumor growth inhibition, allowing for the derivation of an average drug concentration of 44 ng/ml as a requirement for tumor stasis in SJSA-1 per cycle. This value was further adjusted to account for the tumor resistance component in which the tumor cells were less responsive to treatment, as well for rat to human difference in free drug fraction. A structurally similar TGI model but with exponential growth was then utilized for PKPD modeling of the clinical time course of longitudinal tumor SLD data from patients treated with escalating doses of HDM201 and at different treatment schedules. PKPD modeling of clinical data confirmed human tumor size modeling is in line with preclinical modeling projection with a derived average drug concentration of 68 ng/mL required for tumor stasis. These projected concentrations appeared consistent with clinical responses.

Conclusions: For both preclinical and clinical data, tumor size measurements were adequately described by a single consolidated model structure that captured continuous tumor size with a combination of growth regression and resistance terms. Both preclinical and clinical TGI models indicated that average concentration per cycle was a predictor of tumor size response, demonstrating efficacy to be independent on schedule, and allowing for schedule adjustment to identify optimal treatment strategies. This work demonstrates that PKPD modeling can be used for predictive translational pharmacology from nonclinical

to clinical development, helping guide decisions on dose escalation and dosing regimen selection for HDM201 in clinic.

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IV-28: *Nicola Melillo* Variance based Global Sensitivity Analysis of a Physiological Absorption model for compounds in different BCS classes

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Objectives:

There is a strong regulatory interest in the use of sensitivity analysis to evaluate physiologically-based pharmacokinetic models for use in pharmaceutical research & development [1]. One possible application is the prediction of fraction absorbed and bioavailability for drugs following oral administration. The OrBiTo project (Innovative Medicines Initiative) executed a large scale evaluation of various physiological models for drug absorption, where the results showed high variability in the performance [2]. In this context, we performed a variance based global sensitivity analysis (GSA) on an in-house compartmental physiological model for drug absorption, with the aim of identifying key parameters that influence the fraction absorbed. This analysis was done for four different classes of drugs according to the Biopharmaceutics Classification System, differentiating compounds by permeability and solubility.

Methods:

Variance based GSA aims to quantify the importance of each model parameter with respect to a model output *Y*, considering all the parameters in their whole range of variation. Two sensitivity indices are derived by the decomposition of the variance (V) of *Y* [3, 4]. These indices are known as the main effect S_i and total effect $S_{Ti.}$ They are always between 0 and 1. The higher S_i and S_{Ti} are, the more the *i*-th parameter explains *V(y)* and so the more important it is. Conversely, a parameter is considered less important if has low S_{Ti}.

A variance based GSA was performed on an in-house compartmental absorption model, based on the CAT model [5], for neutral, acidic and basic compounds for each of the four BCS classes: class I (highly permeable, highly soluble); class II (highly permeable, lowly soluble); class III (lowly permeable, highly soluble); and class IV (lowly permeable, lowly soluble).

The input parameter that controlled the absorption was the absorption rate constant k_a, that was derived from human effective jejunal permeability, P_{eff}. The cut-off value for P_{eff} that distinguish between high and low permeability was set to 1.5×10^{-4} cm/s, according to [6]. One parameter that could distinguish between high and low solubility is the dose number D_0 [7, 8]. If $D_0<1$ a compound is highly soluble, while if the $D_0>1$ it has low solubility [8].

Results:

Considering the neutral case, for class I drugs given at doses up to 100 mg, the most important parameters for the fraction absorbed were related to the dissolution, whereas for a dose of 1000 mg the key parameters were related to absorption. This could be explained given the fact that within a certain class, drugs administered with higher doses have typically higher solubility, so, for these drugs the rate limiting step is no longer the dissolution, but the absorption.

For class II neutral drugs the most important parameters were always related to the dissolution process. For class III compounds administered at low doses (0.1, 1, 10 mg) a similar situation was observed as for class I drugs, most likely because the dissolution process was not fast enough and became the rate limiting step. At higher doses, an increased importance of absorption processes was observed. This happens because there is an increase in the dissolution and so the rate limiting step becomes the absorption. A more complicated situation was seen for class IV compounds, where parameters related to both dissolution and absorption were always important.

For an acidic drug, the results were similar to the case of a neutral one. For basic compounds the results started to deviate compared to the previous cases. One difference was that the drug's *pKa* became the most important parameter up to doses of 10 mg in class I and for all the doses in classes II and IV. This could happen because, dependent on the value of *pKa*, the solubility in the stomach may be enhanced, compared to the small intestine.

Conclusions:

In mechanistic physiological models we often encounter uncertainty in the parameters values. Typically, when these models are used, there is a tendency to fix some uncertain parameters to their mean value or to use *in silico* methods, such as QSAR models, to predict parameter values, without sufficiently exploring the impact on model development and on predictions.

This work aimed to identify the importance of different parameters for varied types of drugs, to improve the knowledge of the model and inform the choice of what parameters that need to be more carefully considered.

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IV-29: *Johanna Melin* Dapagliflozin pharmacokinetics is similar in adults with type 1 and type 2 diabetes mellitus

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Objectives: Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption, leading to urinary excretion of excess glucose [1]. Since the mode of action is independent of insulin, investigations using dapagliflozin for treatment of patients with type 1 diabetes mellitus (T1DM) with inadequate glycemic control are currently ongoing. A previous analysis indicated that the pharmacokinetic (PK) properties of dapagliflozin is similar in T1DM and T2DM patients [1]. The objectives of the analysis were to characterize the PK of dapagliflozin in T1DM patients, to understand influence of covariates on the PK of dapagliflozin, and to compare PK exposure of dapagliflozin between T1DM and T2DM patients based on phase IIa/III data using a population PK approach.

Methods: The population PK analysis was performed in NONMEM 7.3 [2] using dapagliflozin plasma concentrations in adults with T1DM from 1 Phase IIa study (NCT01498185) and 2 Phase III trials (NCT02268214 and NCT02460978). In total, 5797 samples with quantifiable concentrations from 1151 patients administered 5 mg or 10 mg dapagliflozin up to 24 weeks were used for the analysis. The PK of dapagliflozin was described by a 2-compartment model with first order absorption and linear clearance. Exponential interindividual variability was estimated for apparent clearance (CL/F), apparent central volume of distribution (Vc/F), and apparent intercompartmental clearance (Q/F). The residuals were described by a proportional error model. The effect of covariates on dapagliflozin PK was investigated using stepwise covariate modeling as implemented in PsN 4.4.8 [3]. Non-significant covariates were added at a later stage to evaluate their effect/lack of effect on area under the concentration curve (AUC), which was derived using the Empirical Bayes estimate for CL/F. AUC for T2DM patients from previous studies were extracted and compared to AUC of the current analysis.

Results: The final population PK model adequately described the dapagliflozin concentrations in adult T1DM patients. The estimated CL/F was 20.5 L/h, which was comparable to the previous estimate in adult patients with T2DM and healthy subjects (22.9 L/h). Model-predicted systemic exposure for 5 mg and 10 mg of dapagliflozin was dose-proportional and was comparable between T1DM and T2DM patients. Previously identified covariate relationships in adult T2DM patients and healthy subjects were confirmed in T1DM patients. The identified covariate relationships were: patients with better renal function measured as estimated glomerular filtration rate (eGFR) had higher CL/F, males had higher CL/F and Vc/F than females, heavier patients had higher CL/F and Vc/F, and older patients had lower Vc/F than younger patients. Within the studied range of covariates, no covariates affected systemic dapagliflozin exposure more than 25% compared to the reference individual. Based on previous exposure-response relationship and ongoing investigations in T1DM, no covariates were deemed clinically relevant.

Conclusions: The PK of dapagliflozin in T1DM patients was adequately described by the established population PK model, and no clinically relevant covariates were identified. Moreover, the identified covariates in T1DM patients were similar to the covariates identified in T2DM patients. Systemic dapagliflozin PK exposure in T1DM patients following administration of 5 mg and 10 mg dapagliflozin was

found to be dose-proportional and comparable to the PK exposure of T2DM patients. This confirms that PK properties of dapagliflozin are similar for both patient populations, and suggests that there is no pharmacokinetic reason to adjust doses in T1DM patients.

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IV-30: *Matilde Merino-Sanjuán* Evaluation of the impact of undernourishment on the intestinal absorption of gefitinib in rats.

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Objectives: The influence of undernutrition on the intestinal absorption of gefitinib, a tyrosine kinase inhibitor, has not been previously evaluated. The main objective of the present study was to investigate the impact of nutritional status on gefitinib intestinal absorption in well- and undernourished rats.

Methods: Absorption studies for gefitinib were performed in male Wistar rats in accordance with the 2010/63/EU directive of 22 September 2010 regarding the protection of animals used for scientific experimentation. In order to provoke adequate protein energy malnutrition, the malnutrition protocol developed by Merino-Sanjuán et al. was employed (1). Assayed gefitinib concentrations were 8 µg/mL and 40 µg/mL in free solutions. Additionally, a gefitinib solution (40 µg/mL) with sodium azide (6500 µg/mL) - a metabolic inhibitor - was assayed. All solutions were buffered to pH 5.0 by addition of 1% (V/V) Sørensen phosphate buffer solution. Drug solutions (5 mL at 37°C) were introduced into the proximal and distal isolated intestinal segments. Samples of 200 µL were collected every 5 minutes up to a period of 30 minutes and gefitinib concentrations were determined chromatographically using an HPLC equiped with a UV detector (330 nm) and C18 column. Mobile phase consisted of acetonitrile/water acidified with trifluoroacetic acid (0.1%, pH = 2.5) (55:45). Thereafter, pharmacokinetic models were developed through non-linear mixed effects modelling using the NONMEM software, version 7.3 (2) to describe the intestinal lumen concentration-time profiles.

Results: Data was best described by a Weibull model (3-5), as described by the following equation:

$$dL/dt = -(\alpha \cdot L/\beta) \cdot (t \cdot \alpha)^{\beta-1}$$

where L represents drug concentration in intestinal lumen. The scaling factor α ($hours^{-1}$) is proportional to the slope of the disappearance kinetics, and the shape factor β (dimensionless) determines the curvature of the disappearance kinetics.

A correction fraction (*fr*) was included in the final model to account for the fraction of initial concentration available for absorption from the intestinal lumen to the enterocyte (6). The final model considered an *fr* parameter for the 40 µg/mL gefitinib solution ($fr_{40} < 1$) but not for 8 µg/mL gefitinib solution ($fr_8 = 1$). Statistically significant differences were not found for model parameters and between intestinal segments. On the other hand, parameter fr_{40} proved to be 19% higher for the proximal intestine ($fr_{40} = 0.606$) than for the distal segment ($fr_{40} = 0.510$). Regarding sodium azide administration and undernutrition status, statistically significant differences between groups were not evidenced in model parameters.

Conclusions: The results of the covariate analysis indicated that disappearance-rate of gefitinib from intestinal lumen is not influenced by undernourishment nor by the presence of azide at the used concentration. These results are in accordance with some of the previous studies, which indicate that

gefitinib absorption is not dependent on active transporters and thus the absorption process for gefitinib is most probably governed by a passive diffusion process.

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IV-31: *Jonathan Mochel* Modeling Primary Tumor Growth in a Xenograft Mouse Model of Non-Small Cell Lung Cancer Treated With Pemetrexed-Cisplatin and Bevacizumab

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Objectives: Bevacizumab, an anti-angiogenic drug, is commonly administered along with chemotherapeutic drugs for advanced non-squamous non-small cell lung cancer (NSCLC) [1]. Bevacizumab administration transiently enhances chemotherapeutic drug delivery, resulting in increased treatment efficacy of chemotherapeutic drugs. The objective of this analysis was to characterize the respective efficacy of concurrent vs. sequential administration of pemetrexed-cisplatin and bevacizumab in NSCLC tumor carrying mice.

Methods: 77 xenografted mice were randomized into 5 treatment groups, as follows: i) control (saline, N=15), ii) bevacizumab with pemetrexed-cisplatan 3 days apart (N=16), iii) bevacizumab with pemetrexed-cisplatan 8 days apart (N=15), iv) concurrent bevacizumab with pemetrexed-cisplatan (N=16), and pemetrexed cisplatin alone (N=15). Treatments were administered as single I.P bolus at a dose of 20 mg/kg, 100 mg/kg, and 3 mg/kg for bevacizumab, pemetrexed, and cisplatin respectively. Tumor size was evaluated by whole tumor fluorescence (excitation: 554 nm, emission: 581 nm), and the resulting data were analyzed using the stochastic approximation expectation maximization algorithm implemented in Monolix 2016 R1. Standard goodness-of-fit (GOF) diagnostics, including population and individual predictions vs. observations, and the distributions of weighted residuals were used to evaluate the performances of the final model. Model selection was based on statistical significance between competing models using the objective function value and the Bayesian information criteria, together with the evaluation of GOFs. Residual error estimates from the mathematical models were used as supportive information for evaluation of lack of fit. Normality and independence of residuals were evaluated using histograms and quantile-quantile plots.

Results: Tumor size kinetics in the control group was best described using a revisited Gompertz model governed by parameters α (cell proliferation rate) and β (rate of exponential decrease of the tumor). A proportional error model was used to account for the residual noise in the measurement of tumor size. Bevacizumab increased cisplatin drug delivery by improving the vasculature quality (Q). The dynamics of this improvement was assumed to follow bevacizumab concentrations, delayed by a time τ shift for the normalization to occur. The magnitude of the improvement was controlled by parameter δ. Structural identifiability of the model parameters was further confirmed using sensitivity analyses, the estimated correlation of the random effects (<0.10 for most parameters) and the accurate precision of the final model parameters (RSE<20%). The validity of final model parameter estimates was further confirmed through visual predictive checks using 500 Monte-Carlo simulations.

Conclusions: Our model-based analysis showed that a revisited Gompertzian growth function was predictive for modeling the effect of various scheduling of pemetrexed-cisplatin and bevacizumab in NSCLC tumor carrying mice. The model can be used to anticipate the optimal delay between anti-angiogenesis therapy and chemotherapy, and its dependence on the therapeutic dosing schedule.

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IV-32: *Claudio Monteiro Sousa* An in silico HBV model predicts viral response to the oral non-steroidal carboxylic acid FXR agonist EYP001a.

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Objectives: In line with guidance to FDA to expand the use of trial simulations to support drug development [1], a mathematical model was built to simulate the effect of EYP001a treatment on hepatitis B virus (HBV) replication. EYP001a is a synthetic non-bile acid Farnesoid X receptor (FXR) agonist currently under clinical development for chronic HBV infection and NASH. FXR regulates bile acid metabolism and is a target for liver disease therapies. We aimed at exploring the EYP001a effect on hepatocyte virus and viral markers production.

Methods: The mechanistic model was based on curated knowledge extracted from white and grey scientific literature via the community-driven knowledge management platform (https://githealth.io). The complete model (105 ODEs, 287 parameters) integrated bile acids physiology, cholesterol metabolism, HBV replication and compound mode of action (the latter from EYP001a non-clinical data). The computational model was written and implemented through Novadiscovery's proprietary simulation framework and its various tools (SimWork). The SimWork virtual population and exploration tools were used for calibrating the model: virtual patients were randomly generated from ranges of descriptor (representing the n model parameters) values and were selected on the basis of a score translating physiological and biological constraints that the model should comply with; this results in a n-dimension space domain where the parameter values meet the constraints. SimWork was also used for the generation of 10,000 HBV infected virtual patients. An independent team, blinded to available clinical EYP001a data, simulated the effect of single and multiple oral doses of EYP001a in healthy or chronically infected HBV virtual subjects. EYP001a effects on FXR response markers 7α-Hydroxy-4-cholesten-3-one (C4) and Fibroblast growth factor 19 (FGF19) were explored. Model performance was tuned with data observed in healthy subjects and simulated results were validated with data from both in vitro HepaRG experiments and in vivo HBV infected subjects. The effect on HBV replication of several combinations of EYP001a dosing regimens were explored. Additionally, different associated daily dietary intakes of cholesterol schemes were tested. HBV DNA and the surface antigens of the hepatitis B virus (HBsAg) output curves were generated for 10,000 virtual HBV subjects treated during 100 days with EYP001a.

Results: The model successfully predicted EYP001a plasma concentration-time profiles (Cmax, Tmax and AUC) at the different tested doses and regimens. The model reproduced accurately the dynamics of blood viral particles, C4 and FGF19 and their changes after single and multiple EYP001a administrations and predicted HBsAg levels. Comparison of in silico HBV DNA and HBsAg outputs indicated that prolonged, but not short lasting FXR agonism with EYP001a inhibited viral replication. Various combinations of dosing regimens with associated cholesterol dietary intakes were tested and it was established that 200mg EYP001a BID was an appropriate efficacious regimen.

Conclusions: The in silico model predicted well EYP001a plasma concentrations and pharmacodynamic response in a virtual HBV infected population. The strong predictability of our simulation approach using in silico modeling could be used to determine an a priori better dosing regimen in chronic HBV patients. This

in silico model will be used to explore other FXR agonist treatment strategies and to identify best responders in the population to be tested in phase II HBV trials.

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IV-33: *Denise Morris* Population Pharmacokinetic Modeling of Fremanezumab in Support of Phase 3 Development for Patients with Migraine

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Objectives: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide, was found to be effective and well-tolerated as a preventive treatment for migraine in Phase 2 and 3 studies. Modeling and simulation were used to develop a population PK model in healthy subjects and patients with episodic or chronic migraine.

Methods: The population PK analysis, performed using NONMEM, included data after subcutaneous administration from 1 richly sampled Phase 1 study (TV48125-PK-10078 [225, 675, and 900 mg single dose]), 2 sparsely sampled Phase 2b studies (LBR-101-021 [675-225-225mg monthly or 900mg monthly for 3 doses]; LBR-101-022 [225 mg or 675 mg monthly for 3 doses]), and 3 sparsely sampled Phase 3 Studies (TV48125-CNS-30049 [675 mg followed by monthly doses of 225 mg for 3 doses or single 675 mg once quarterly]; TV48125-CNS-30050 [225 mg once monthly for 3 doses or single 675 mg once quarterly]; TV48125-CNS-30051 [225 mg monthly or 675 mg followed by 225 mg monthly or 675 mg once quarterly over 12 months]). The final PK model was validated using prediction-corrected VPC (pcVPC). PK simulations were performed, and calculated exposures were generated based on the final PK model and individual Bayesian estimates of PK parameters assuming a pre-determined set of dosing regimens: 225 mg once monthly for 12 doses; 675 mg loading followed by 225 mg once monthly for a total of 12 doses; 675 mg quarterly for 4 doses.

Results: A total of 8346 fremanezumab concentrations from 2287 individuals were used for the population PK modeling. A 1-compartment model with first-order absorption and elimination adequately fit the pooled Phase 1/2b/3 data. Following covariate analysis, an effect of body weight on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F) was included in the model. Age, albumin levels, CrCL, sex, race, as well as acute and preventive medications were also tested as covariates and not found to be statistically significant predictors of variability in PK. Anti-drug antibodies (ADA), analgesic migraine specific medication, and liver function were not tested in the covariate analysis as too few patients were present in the population. All parameters were estimated well, with no high correlations between parameter estimates. Bayesian shrinkage was below 30% for CL/F and Vc/F. Eta shrinkage for k_a was higher (52%), due to lack of information on the absorption phase in the sparsely sampled patients. For the Phase 1 data, the pcVPC showed a small degree of overprediction around the peak for the Phase 1 data with some underprediction during the post-absorptive phase of the profile. At almost all sampling time points for the Phase 2b/3 data, the pcVPC showed good concordance between observed and simulated data. Higher weight was associated with increased clearance and central volume of distribution resulting in a decrease of fremanezumab exposure. Simulated exposure measures were marginally higher (although overlapping) in female subjects compared to males; Asian subjects compared to other races; and subjects using acute migraine specific medication compared to those that were not. For age, patient status (healthy versus migraine), and preventive/analgesic migraine specific medications, simulated exposures were similar across comparable groups. Although median values for model-predicted exposures tended to be slightly lower in individuals who tested positive for ADA, the range of exposures for these individuals were fully contained within the range of exposures for individuals who tested negative for ADA. Based on simulated data, the estimated median half-life for fremanezumab is 31 days and steady state is expected to be achieved by

approximately 168 days for monthly and quarterly doses. The use of 225 mg monthly with a starting dose of 675 mg resulted in faster achievement of plasma concentrations within the steady state range. The median accumulation ratio, based on once-monthly and once-quarterly dosing regimens, was approximately 2.34 and 1.20, respectively.

Conclusions: A 1-compartment model with first-order absorption and elimination and body weight effect on CL/F and Vc/F adequately described the fremanezumab concentration-time data. Body weight was the only significant predictor of variability in PK with increases in body weight resulting in decreased fremanezumab exposure. The half-life and accumulation ratio support once monthly and once-quarterly dosing of fremanezumab.

IV-34: *Ricardo Nalda-Molina* Population Pharmacokinetics of Hyperthermic Intraoperative Peritoneal Oxaliplatin in Wistar Rats

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Introduction and Objective: Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is part of a multidisciplinary treatment proposed for patients suffering from peritoneal carcinomatosis. The evaluation of the efficacy and toxicity of HIPEC technique presents some difficulties, due in part to the lack of information about the pharmacokinetic (PK) behavior of the drugs administered in this procedure. Development of suitable animal models contributes to evaluate the impact of the multiple components in HIPEC separately and gives useful information for future clinical research. A significant impact of the dose, temperature and instillation time on PK parameters may significantly affect the plasma concentration profile and, therefore, the Area Under the plasma concentration-time Curve (AUC_{pla}).

Therefore, the aim of this study was to characterize the population pharmacokinetics of hyperthermic intraoperative peritoneal oxaliplatin (HIPEO) in Wistar rats and to evaluate the effect of treatment-related covariates dose, instillation time and temperature on the pharmacokinetic parameters.

Methods: Rats were randomly allocated in six groups (G1-G6) and submitted to different experimental conditions of temperature, instillation time or dose. As a common procedure, all of rats underwent an intraperitoneal hyperthermic instillation (LIHI) with 100 mL of 5% dextrose solution under anesthetic conditions. Out of them, 36 were assigned to receive HIPEO administration, carried by the heated 5% dextrose solution, as used in HIPEC procedure. In addition, to allow determination of the fraction of dose absorbed (F), six rats of one additional group (G7) were administered with one dose of intravenous (IV) oxaliplatin undergoing LIHI procedures, without adding oxaliplatin in the instillation solution. This procedure ensured that IV administrations were done at similar surgical conditions to the HIPEC groups. Plasma samples were taken immediately after the IV or peritoneal oxaliplatin administration and at times 1, 10, 20, 30, 45, 60, 90, 150, 270 and 510 minutes. Samples were frozen after centrifugation until their analysis by graphite furnace atomic absorption spectrophotometry. The plasma concentrations profiles for all the groups were analyzed together with a nonlinear mixed effects model (NONMEM software v7.3). The impact of dose, temperature and instillation time on the PK parameters was explored. The graphs and statistical calculations were performed using the R software v3.3.2. Bootstrap analysis was conducted to calculate 95% confidence interval for final model parameter estimates and relative standard errors of estimate (%RSE) after generating 1000 datasets by resampling with replacement method (Wings for NONMEM program). Model validation was performed by visual analysis of goodness of fit plots and prediction-corrected Visual Predictive Check (pcVPC).

Results and Discussion: Intraperitoneal (n=115) and plasma (n=263) concentrations were successfully described according to a two-compartment model with first order absorption. No significant effect of dose, temperature and instillation time on pharmacokinetic parameters was found. However, an abrupt decrease in the elimination process was observed, reflected in the structural pharmacokinetic model through a modification in clearance. The typical parameters values and the interindividual variability (CV %) in clearance, central and peripheral volume of distributionwere 3.25 mL/min (39.1%), 53.6 mL (37.8%) and

54.1 mL (77.3%), respectively. Clearance decreased to 0.151 mL/min (39.1%) when the instillation was still ongoing, at 31.4 minutes, probably caused by the alteration of renal function attributed to surgery procedure and/or hyperthermia.

Conclusion: This study described the deterioration of the drug elimination process due to the procedure, and estimated the time at which this deterioration is most likely to occur. In addition, dose, instillation time and temperature had no influence in the PK parameters.

IV-35: *Antonina Nikitich* Immune Response Template for Quantitative Systems Pharmacology Modeling: Description of Co-inhibitory and Co-stimulatory Receptors Interaction

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Objectives: Immunotherapy is a new class of cancer treatment that works by activation of immune response of patient to fight with tumor. Antibodies targeting co-inhibitory and co-stimulatory receptors expressed on the surface of immune and cancer cells are one of the most promising and effective type of immunotherapies used to treat cancer. The main aim of this study is to develop a platform facilitating the development of checkpoint inhibitors (antibodies targeting co-inhibitory receptors) and agonists of co-stimulatory receptors.

Methods: Immune Response Template (IRT) platform was developed. IRT is ordinary differential equations based model describing immune system in humans. It includes various cell types (CD4 and CD8 T cells, different types of macrophages (M1, M2a, M2b, M2c), B cells, dendritic cells, natural killer (NK) cells, myeloid-derived suppressor cells (MDSC), etc.), processes (antigen presentation, specific lysis, activation, differentiation, proliferation, etc.), mediators (TGF beta, IFN gamma, TNF alpha, IL-2, IL-6, IL-10, IL-12, etc.), and co-inhibitory and co-stimulatory receptors (TCR, CD3, MHC-I, MHC-II CD28, CD86, CTLA-4, PD-1, PD-L1, LAG3, TIM-3, GITR, OX40, 4-1BB etc.) involved in tumor progression and treatment. The interaction of surface molecules were described in framework of immunological synapse between different types of immune cells (for example, interaction of CD4 T cells and dendritic cells) and between immune cells and cancer cells (for example, interaction of CD8 T cells and tumor cells). Part of the developed model including CD4 T cells, dendritic cells and immunological synapse between them, was used to describe in vitro data on effect of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) combination on IFN gamma production by CD4 T cells stimulated by autologous dendritic cells [1].

Results: Model was developed and calibrated. Parameters were identified on the basis of published in vitro and in vivo data. Description of co-inhibitory and co-stimulatory receptors in framework immunological synapse takes into account the conformation and valency of receptors (for example, CTLA-4 is bivalent homodimer, i.e., it exists as dimer and each monomer is able to bind with other receptors). Developed model allows to describe increase in IFN gamma production by CD4 T cells cultured with autologous dendritic cells in presence of different concentrations of nivolumab and ipilimumab [1]. Model was able to describe variability in response to nivoloumab/ipilimumab combination by cells obtained from different subjects. The variability was described by changing value of one parameter.

Conclusions: Developed model takes into account the interaction of co-inhibitory and co-stimulatory receptors in framework of immunological synapse between immune cells or immune cells and cancer cells. Model is able to describe the data on checkpoint inhibitors effect on CD4 T cells activation by dendritic cells including the variability in response. Developed platform could be used as tool to investigate and optimize immunotherapies for cancer treatment including combination of checkpoint inhibitors.

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IV-36: *Asbjørn Nøhr-Nielsen* A review of fixed-dose combination approvals in the EU based on European public assessment reports (EPARs)

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Introduction: Fixed dose-combination (FDC) products, a subset of combination therapies, contain a fixed ratio of two or more active ingredients with distinct modes of action formulated into a single dosage form. FDC products contribute to treatment regimens with unique advantages compared to conventional monotherapies by providing an enhanced clinical efficacy and safety profile, improved patient compliance and convenience, and opportunities for development of novel treatment entities through synergistic action of the components[1–3]. From a regulatory perspective, FDC products are subject to separate regulations by the US Food and Drug Administration (FDA), European Medicines Agency's (EMA), and the WHO[4–6]. The EMA guidelines specify that it is required by the applicant to demonstrate that each active substance contributes to efficacy and/or benefit-risk balance. To achieve this it is suggested to perform a factorial design study – at least when pursuing the add-on or initial treatment indications outlined in the Guideline on clinical development of fixed combination medicinal products[6]. However, it could be questioned whether a consequence of these comprehensive recommendations for FDC products is that excessive investigations with factorial design are being performed[7].

Objectives:

- Assess the body of evidence submitted with a Marketing Authorization Applications (MAAs), with a specific focus on the characteristics and indications of the FDC products as well as the number and size of clinical trials conducted.
- Examine approaches applied during the clinical development, specifically the dose selection process, clinical trial design, and the use of pharmacokinetic-pharmacodynamics modelling.

Methods: The main resource for this study was the European public assessment reports (EPARs), which are published by the EMA and are publicly available online[8]. The present study included applications with authorization date from January 2010 to December 2016 and considered only the applications in which the drug product contained two active substances. Neither products that were refused approval by the CHMP nor products that were withdrawn after market authorization were considered. Additionally, products that were considered either generic, biosimilar, vaccine or orphan products were considered to be outside the scope of this review and were therefore excluded. Statistical analyses were performed using R 3.4.3 for windows[9], supplemented with the R package "geepack" for generalized estimation equations[10]. A full model approach was used, containing four separate response variables (trials, arms, patients, and doses tested) and six predictor variables (ATC code/design, clinical trial phase, FDC type, PK-PD modelling and number of approved FDC doses).

Results: The bulk of clinical evidence for FDC products is found in phase III as many sponsors seem to put less emphasis on phase II trials. For FDC type there was a clear increase in trials, arms and patients for two approved drugs compared to those that included one or two new molecular entities, however, this increase was not seen for doses tested. More than half of FDC products composed of two previously approved components were approved without a dose finding trial. Certain types of PK-PD modelling had a significant

effect on the number of doses studied. Lastly, for clinical trial design we found that significantly more patients are included for factorial design compared to ray design.

Conclusion: These finding suggest that a factorial design study should be carefully considered as a ray design could provide similar information using far less patients. Furthermore, sponsors could consider greater emphasis on phase II and employing the use of PK-PD modelling in order to have a greater pool of information available when designing the larger phase III studies, thereby grouping patients on fewer combination doses, increasing the likelihood of showing superiority of the combination over the individual components. This is especially true for combinations of two previously approved drugs, as the data showed equally many combination doses tested for these FDC products as those containing one or two new molecular entities.

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IV-37: *Patrick Nolain* PopkinR: a suite of Shiny applications focused on the pharmacometrics workflow

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Introduction: Pharmacometrics workflow can be defined by a succession of well-defined tasks ranging from exploratory data analysis, modeling (execution, diagnostics, validation, simulation) and communication. Although each of these steps often require dedicated software and technologies, they share common needs (e.g. data visualization, reporting) which could take benefit from interactive analyses. The recent growth of data science related tools in R[1], in particular the web-application framework Shiny[2], brings new opportunities for the development of tools facilitating these activities.

Methods: A suite of interactive web-applications was developed to help the processing of several stages of a pharmacometric analysis using R and the shiny package.

Results: The PopkinR suite consists of four main components (already available):

- PMXplore: an exploratory data analysis application of NONMEM-like datasets
  Provides interactive visualizations and summaries of various data types (dependent variables, dosing regimens, covariates) and dataset manipulation functionalities.
- PMXrun: a NONMEM runs management application
  Within the Sanofi computing cluster environment (Popkin[3]), pilots the execution of single (new or based on a prior run) or batch runs (e.g. initial values search, sensitivity analysis, covariates screening, bootstrap), monitors estimation convergence and supervises the cluster load in real time.
- PMXploit: an R package for NONMEM post-processing analysis
  The embedded shiny application allows pharmacometricians to interactively analyze NONMEM runs: obtain summaries of estimation results (e.g. convergence, parameter estimates, precision, shrinkage), visualize plots on the fly (e.g. observed data, goodness-of-fit, parameters and covariates distributions and correlations), compute numerical quality criteria, detect outliers, generate Visual Predictive Checks and compare multiple runs results. Generated plots and tables can easily be integrated into reports as well as splitted and filtered for subgroups analyses.
- SimShiny: dynamic model-based simulations applications for communication of modeling results

Following the development of a model, a dedicated SimShiny application is designed to perform dynamic simulations and visualize model predictions. Model equations are implemented in R (using mrgsolve[4] or RxODE[5] packages) and user interfaces are adapted to each particular situation like comparison of dosing scenarios, computation of exposure parameters, comparison to models from the literature or exploration of complex dynamical systems. These tools facilitate communication of modeling results and foster collaboration with non-modelers, increasing the visibility of pharmacometry and its contribution to decision-making.

Conclusions: A suite of web-applications dedicated to several steps of pharmacometrics workflow, from data exploration to simulation-based decision making, was developed. PopkinR shows the ability of interactive applications to improve the efficiency of pharmacometricians' work and the communication of

modeling and simulation contribution to a wider audience to support drug development. Two additional components (a non-compartmental analysis and a therapeutic drug monitoring applications) are in development to complete the PopKinR suite.

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IV-38: *Rikard Nordgren* Faster methods for case deletion diagnostics: dOFV and linearized dOFV

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Objectives: Case deletion diagnostics (cdd) is a method for finding individuals that are especially influential on a model estimation. The standard way of performing a cdd for non-linear mixed effect models (NLMEM) is to exclude one individual at a time and reestimate the model. Typically the cook score and the covariance ratio have been used as metrics for the individual influence on the parameter estimates [1, 2]. Both these metrics require the covariance matrix of the parameter estimates which might be difficult to obtain. More importantly, the usefulness of the cdd is diminished by the fact that it is relatively slow as it requires one full NLMEM estimation per individual. Here we propose a new metric, delta-OFV (dOFV), to assess the influence on the total model fit and evaluate it for a set of models. This metric does not rely on the covariance matrix. Furthermore, the switch to the dOFV metric also allows to use linearized models which can substantially reduce runtime.

Methods: The dOFV metric was calculated for each case deleted run separately and was defined as the difference between the OFV of the full run adjusted for the removed individual and the case deleted run. Let OFVall be the OFV for the run with all individuals and iOFVk be the individual OFV for subject k in that run. Furthermore, let OFVk be the OFV from the run with individual k removed, then dOFV was calculated as dOFV = OFVall - iOFVk - OFVk.

The dOFV based cdd was performed both using the NLMEM as well as using a linearization approximation of the model [3,4] and compared to a cook score based cdd. Additionally, the runtimes of the non-linear dOFV cdd, the linearized dOFV cdd and the cook score based cdd were compared.

All comparisons of the different metrics and runtime were done for 15 different pharmacometric models using PsN 4.7.16 and NONMEM 7.4.2.

Results: The graphic comparison between dOFV and cook score showed a slight non-linear relation and the Pearson (linear) correlation coefficient ranged between 0.46 and 0.78 for the tested models.

The comparison of dOFV with linearized dOFV for the 15 models shows a correlation between 0.67 and 1.0 with an average of 0.92. Setting a cutoff for influential individuals to 3.84 displayed only one missed influential individual in the linearized cdds and no false influential individuals.

Speedup for non-linear dOFV cdd versus the cook score based cdd was between slightly above 1 up to 1.8 for the tested models. The average speedup for the linearized models with short runtimes (below 1000 s) was, due to a high proportion of overhead, only 2.4, but was for the models with long runtimes (above 1000 s) 973.

Conclusions: The dOFV based cdd showed promising performance with large agreement with the traditional cook score based cdd but shorter runtime and without relying on the covariance matrix. Model linearization led to large reductions in runtime without a big impact on the dOFV cdd results. Given our experiments the risk of missing an influential individual exists but is low.

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IV-39: *Ana Novakovic* Simulation based assessment of flat dose regimen of an anti-PDL1 antibody: Case study of avelumab

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Objectives: Avelumab is a human anti–PD-L1 IgG1 antibody that has demonstrated meaningful efficacy and clinical activity across various tumor types with a manageable safety profile. Avelumab 10 mg/kg IV every two weeks (Q2W) is approved in the US, EU and Switzerland for treatment of metastatic Merkel cell carcinoma (MCC), in Japan for curatively unresectable MCC, and for advanced or metastatic urothelial carcinoma (UC) in the US (1), and is in clinical development for other cancer types. In the case of monoclonal antibodies, a flat dose regimen (independent of body weight) is likely to minimize drug wastage, facilitate preparation and administration, and reduce pharmacy errors in comparison to body weight dosing. In addition, a flat dosing regimen is expected to result in more consistent exposure across patient populations, when the power exponent describing the effect of body weight on clearance (CL), using population PK models, is estimated to be less than 0.5 (2). The choice of the flat dose to be considered (800 mg) was based on median body weights of the advanced or metastatic UC and mMCC patients treated with avelumab and general populations of patients with cancer. The objectives of this analysis were to compare avelumab exposure between weight-based (10 mg/kg Q2W) and flat (800 mg Q2W) dosing regimens using simulations based on two population PK models (PK CYCLE and PK SS) describing avelumab PK after single (3) and multiple dose infusions (4). Time-varying CL was introduced to adequately describe the data across all cycles of avelumab treatment. Body weight was found to be a significant covariate on clearance and central volume of distribution. The estimated magnitudes of weight exponents on CL are 0.335 (95% CI: 0.277-0.393) for the PK CYCLE model and 0.324 (95% CI: 0.260-0.388) for the PK SS model.

Methods: Data from 1827 patients across three clinical trials were used for modeling, all given the weight based dosing regimen (dose of 1, 3 or 10 mg/kg Q2W). PK CYCLE and PK SS models were used to simulate exposures for weight-based dosing and flat dosing regimens. A total of 10,000 subjects were simulated taking into account both parameter uncertainty and inter-individual variability. Sets of covariates (including body weight) were resampled from the original data set, with all covariates present in the final model retained at the subject level. Various PK exposure metrics, including maximum serum concentrations (C_{max}), minimum serum concentrations (C_{trough}), and area under the serum concentration-time curve (AUC) after a single dose and at steady state, were simulated for both dosing scenarios and summarized across the entire weight range and by quartiles of weight.

Results: Simulations of exposure comparing weight-based (10 mg/kg Q2W) and flat dosing (800 mg Q2W) after the first cycle (PK CYCLE) and at steady state (PK SS) suggested that the overall variability in exposure was lower for the flat dosing group (coefficient of variation (CV) = 27.1% vs 29.0% for $AUC_{0\text{-}336h}$; 38.6% vs 41.2% for AUC_{ss}). The flat 800 mg dose resulted in slightly higher exposures for the simulated population with the median increasing by approximately 12% and 11% for $AUC_{0\text{-}336h}$ and AUC_{ss}, respectively. For weight-based 10 mg/kg dosing, the lowest weight quartile is associated with the lowest exposure. The opposite is true for the flat 800 mg dose where the highest weight quartile is associated with the lowest exposures. Simulations based on other exposure metrics confirm the results presented here with AUC.

Overall, the simulated exposure for the 800 mg flat dosing regimen fell within the exposure range of avelumab known to be clinically effective and safe.

Conclusions: Modeling and simulation-based analyses were performed to simulate PK exposure for the currently approved 10 mg/kg Q2W and the proposed flat 800 mg Q2W dosing regimens. Predicted PK exposures were similar. Lower variability was observed for flat dosing compared to weight-based dosing, as expected for monoclonal antibodies with weight exponent on CL estimated to be less than 0.5, according to findings from Wang et al. (2). Given the results of these simulations, 800 mg flat dose of avelumab should result in similar exposures and thus maintain the positive benefit risk profile of avelumab while simplifying administration. A flat dose regimen is currently being implemented in several trials.

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IV-40: *Eric Novik* Stan: an open source probabilistic programming language for high-performance statistical computing

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Generable Inc.

Introduction:

Stan (http://mc-stan.org/) is an open source platform for statistical modeling and high-performance statistical computation [1]. Users rely on Stan for statistical modeling, data analysis, and prediction in the biological, social, and physical sciences, engineering, and business.Users specify log density functions in Stan's probabilistic programming language and get: full Bayesian statistical inference with MCMC sampling (NUTS, HMC)approximate Bayesian inference with variational inference (ADVI)penalized maximum likelihood estimation with optimization (L-BFGS)Stan's math library provides differentiable probability functions and linear algebra (C++ autodiff). Additional R packages provide expression-based linear modeling, posterior visualization, and leave-one-out cross-validation.

Objectives:

- Ability to express arbitrarily complex statistical models including models with ODEs
- Stan's implementation of Hamiltonian Monte Carlo and its ability to efficiently sample from high dimensional distributions making comparisons to Random Walk Metropolis and Gibbs sampling as well as Penalized Maximum Likelihood estimation

Methods:

Most people use Stan for specifying statistical models in the Stan language and fitting them with full Bayesian inference using Stan's implementation of Hamiltonian Monte Carlo [2]. In drug development, Stan is being used in Pharmacometrics where the ODE solvers exposed in the Stan language are used to express the model for the conditional mean of PK PD models. See, for example, Weber et al. [3].

Stan's language offers the users a high level interface for specifying statistical and mechanistic models. Stan is a turing complete language, which means that Stan is able to compute any computable function. This offers the level of (almost) arbitrary flexibility allowing users to express, for example, deep hierarchical models (mixed effects) with site specific effects and ODE based patient level effects, and so on.

Stan contains a very efficient implementation of Hamiltonian Monte Carlo (HMC) which allows it to sample from analytically intractable, non-conjugate posterior distributions with complex geometry in high-dimensional parameter spaces. For instance, we fit Stan models with over a million parameters. HMC with NUTS is a modern sampling algorithm which relies on the geometry of the posterior distribution (gradients) to guide the sampling process and scales wells with the number of parameters.

Results:

Stan's performance has been evaluated in extensive simulations and on the real world datasets in many industries including Pharma and drug development. In the original NUTS paper [2] Section 4 empirical evaluations are reported. The efficiency is evaluated in terms of effective sample size (ESS) normalized by

the number of gradient evaluations. In total, we ran 3,200 experiments with HMC and 600 experiments with HMC-NUTS. ESS of a sample is a measure of how many independent samples a set of correlated samples is worth for the purposes of estimating the mean of some function; a more efficient sampler will give a larger ESS for less computation. The algorithm was evaluated on 250-dimensional multivariate normal (MVN) with highly correlated posterior distribution comparing HMC-NUTS (Stan's default), Random Walk Metropolis (RWM), and Gibbs sampling. NUTS was run with $\delta = 0.5$ for 2,000 iterations, with the first 1,000 iterations being used as burn-in and to adapt. This required about 1,000,000 gradient and likelihood evaluations in total. We ran RWM for 1,000,000 iterations with an isotropic normal proposal distribution. The cost per iteration of RWM is effectively identical to the cost per gradient evaluation of NUTS, and the two algorithms ran for about the same amount of time. Weran Gibbs sampling for 1,000,000 sweeps over the 250 parameters. In summary, RWM has barely begun to explore the posterior space. Gibbs does better, but still has left parts of the space unexplored. NUTS, on the other hand, is able to generate many effectively independent samples.

Conclusions:

Stan is a relatively new programming language but it has demonstrated good performance compared with previous generation of probabilistic programming languages like BUGS and JAGS. In particular Stan scales well in high dimensions, does not require conjugacy, offers ODE solvers, and allows for specification of arbitrary complex statistical and mechanistic models often found in Pharmacometrics.

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IV-41: *Katharina Och* A pharmacokinetic/pharmacodynamic model of cyclosporine A and its nephrotoxicity in patients after hematopoietic stem cell transplantation

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Objectives: Development of a pharmacokinetic/pharmacodynamic (PK/PD) model of Cyclosporine A (CyA) in patients after hematopoietic stem cell transplantation (HSCT) with regard to its nephrotoxic potential.

Methods: Data derived from therapeutic drug monitoring (TDM) at the department of Internal Medicine I at the Saarland University Hospital (UKS) was used for model building. All subjects received HSCT due to different underlying malignancies with a majority of acute myeloid leukemia (AML; 72%). CyA was administered once daily as a 24-hour infusion from the day prior to HSCT (day -1). Later on, patients received CyA as an oral administration twice daily. Plasma concentrations of CyA and serum creatinine were measured once daily. For the pharmacokinetic model of CyA, an evaluation of different models from literature was done. Whereas the pharmacodynamics were built by linking the plasma concentration to creatinine clearance as marker for glomerular filtration rate (GFR). Data were analyzed by non-linear-mixed-effects modelling (NLME) using the software NONMEM® (version 7.3.0) and the graphical interface Pirana (version 2.9.7). Moreover, statistical evaluation was performed within the software R (version 3.4.1) and its graphical interface RStudio (version 1.0.143).

Results: The dataset included 32 subjects with 862 observations presenting plasma concentrations of CyA and 1046 observations of creatinine clearance. Pharmacokinetics were described properly by a two-compartmental model with lag time [1]. Its stochastical submodel consisted of a proportional error model and interindividual variability on all used parameters (clearance, central volume of distribution, peripheral volume of distribution, intercompartmental clearance, rate of absorption and bioavailability). In order to describe changes in GFR it was necessary to treat GFR as a formation product with synthesis rate and degradation rate. A turnover model with zero order synthesis rate (k_{syn}) and first order degradation rate (k_{deg}) fitted best. Here, k_{syn} (0.09 (ml/min) $*h^{-1}$) was independent of k_{deg} (0.0015 h^{-1}). The concentration of CyA had a significant impact on the inhibition of GFR synthesis rate. This influence was described very well as an Emax model with great Hill coefficient (Hill = 40) representing a steep concentration-effect relationship. The stochastical submodel included an interindividual variability on k_{syn} and an additive error as residual error. Different attributes (e.g. age, gender, underlying disease, conditioning regime) were tested as covariates but none of them had a significant impact.

Conclusions: The pharmacokinetic/pharmacodynamic model represented the quantitative relationship between Cyclosporine A exposure and its nephrotoxicity. Considering the steep concentration-effect relationship an on-off switch of the nephrotoxic effect of CyA can be assumed. While the model fits the data further research has to be done in order to improve and validate the model in a lager cohort. A valid PK/PD model could be used as a tool to investigate the nephrotoxic potential of CyA or even as a clinician's tool to monitor the nephrotoxic risk in patients under treatment with CyA.

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IV-42: *Chika Ogami* Population pharmacokinetics of unbound daptomycin in hospital patients with Gram-positive infections

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Objectives: Daptomycin is a lipopeptide antimicrobial agent that exhibits bactericidal activity against a broad range of Gram-positive bacteria, including multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus*. The clinical benefit of daptomycin is dependent on adequate drug concentrations however the risk of inducing creatine phosphokinase elevation is increased in patients with blood concentrations greater than 20 mg/L [1, 2]. Daptomycin is primarily excreted renally and dose adjustments are recommended in patients with renal impairment [3]. In this study, we evaluated the pharmacokinetics of unbound daptomycin based on population pharmacokinetic approaches.

Methods: Routine clinical data including daptomycin concentrations were collected from 52 patients with Gram-positive infections. The pharmacokinetics of daptomycin were described with a zero-order input, two compartment distribution and first-order elimination model. Pharmacokinetic parameters were estimated based on observed daptomycin unbound concentrations (n = 339) and fraction unbound in plasma was estimated from total (n = 329) and unbound concentrations. Normal fat mass (NFM) was used as the body size index and pharmacokinetic parameters were standardized to total body weight of 70 kg height of 1.76 m [4]. Renal function (RF) was described by the ratio of observed creatinine clearance standardized to total body wright of 70kg to standard creatinine clearance of 6 L/h/70kg.

Results: The pharmacokinetic parameters for unbound daptomycin CL, VC, VP, Q and Fu (fraction of unbound) were:

CL (L/h) = (2.94 × 0.544^HD + 6.00 × RF) × (NFMCLobs/NFMCLstd)^3/4

VC (L) = 167 × 0.643^HD × (NFMVobs/NFMVstd)

Q (L/h) = 0.879 × (NFMCLobs/NFMCLstd)^3/4

VP (L) = 65.2 × (NFMVobs/NFMVstd)

Fu = 0.0946 × 1.27^HD

HD represents hemodialysis with a value of 1 in patients who received hemodialysis and 0 in those who did not. The elimination half-life for unbound daptomycin calculated from the estimated population mean of clearance and volume of central and peripheral compartment was 18.0 h. Clearance of daptomycin was estimated to be about 60% dependent on renal function. The influence of hemodialysis was incorporated into non-renal clearance and unbound volume of distribution. Both these pharmacokinetic parameters were decreased in patients with hemodialysis. The fractions of unbound daptomycin was estimated to be 0.0946 and increased by 1.27-fold in patients receiving hemodialysis. Ffat included in NFM as the factor describing the influence of fat mass on clearance was not significantly different from 1 and Ffat for volume

of distribution was not significantly different from 0. This indicates that total body weight is the best predictor of allometric size for clearance and fat free mass is the best predictor for volume of distribution [4].

Conclusions: We have described the influence of renal function, body size and composition and hemodialysis on the pharmacokinetics of unbound daptomycin. This model can be applied to wide range of patients including elderly, obesity, and renal insufficiency. These factors should be considered for dosing regimens in individual patients with Gram-positive infections.

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IV-43: *Boram Ohk* Population pharmacokinetics of sumatriptan in healthy korean subjects : sex differences

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Objectives:

Migraine is a chronic, disabling neurological disorder with episodic clinical findings of headache, often associated with nausea and vomiting. Sumatriptan is a 5-hydroxytryptamine (5-$HT_{1B/1D}$) receptor agonist, which is a one of the most commonly used triptans for treatment of migraine. Sumatriptan acts as a vasoconstrictor of detailed intracranial blood vessels and, also as an inhibitor of the pro-inflammatory neuropeptide release to relieve migraine headache. Epidemiological studies on migraine have consistently shown that migraine is far more common among women than men. In addition, the results that frequency, severity, and type of migraine with greater consequent disability were different between women and men are reported. But the mechanisms behind sex differences are still poorly understood. In this study we focused on the sex differences in the population pharmacokinetics of sumatriptan in healthy Koreans.

Methods:

This study was conducted in 38 healthy volunteers (male: 29, female: 9). All subjects were received 50 mg sumatriptan. Blood samples for pharmacokinetic profiles were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours after dosing. Plasma sumatriptan concentrations were analyzed using ultra-performance liquid chromatography mass spectrometry mass spectrometry (UPLC/MS/MS). A population PK analysis was conducted using NONMEM (Version 7.3, Icon Development Solution, Ellicott City, MD, USA). The dataset consisted of a total of 532 sumatriptan concentration measurements.

Results:

A one-compartment model with first-order elimination, and combined transit compartment model and first-order absorption with lag time was chosen to describe the PK of sumatriptan. Demographic variables and creatinine clearance, calculated with the Cockcroft-Gault equation, were screened as potential covariate for PK parameters. The screening process was performed using visual and numerical approaches. The covariate analysis showed that sex significantly ($p < 0.01$) influenced the clearance (male: 429 L/h, female: 330 L/h) of sumatriptan. For model evaluation, graphical diagnostics (basic goodness-of-fit plot and other accessory plots) were used for single run based diagnostics during model development. The robustness and the predictive performance were evaluated using bootstrapping and the visual predictive check(VPC). A bootstrap procedure was conducted with a total of 1,000 bootstrap-resampled datasets from the original dataset. The median and 90% confidence intervals (CIs, 5^{th} and 95^{th} percentiles) of parameters obtained from this step were compared with the final parameter estimates. Results from the VPC with 1,000 simulations were assessed by graphical comparison of the 90% prediction interval from the simulated data with an overlay of the raw data.

Conclusions:

In conclusion, a population PK model was successfully developed and reasonable parameters were obtained. The enhanced recognition to sex differences will help to understand migraine and may help guide the direction of future headache research.

IV-44: *Andrés Olivares-Morales* Switching from immediate release to modified release can have an impact on intestinal drug-drug interactions: A PBPK simulation study using oxybutynin as a case example

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Objectives: A recently published absorption physiologically-based pharmacokinetic (PBPK) model was used and applied to mechanistically predict the oral bioavailability differences observed for oxybutynin's (OXY) OROS formulation compared to its immediate release (IR) tablet [1]. The PBPK model predictions suggested that the higher bioavailability observed for the OROS formulation was due to a reduced CYP3A-mediated intestinal metabolism. This highlighted the fact that while the distal absorption from the OROS formulation significantly reduced OXY's fraction absorbed (f_a), the decreased abundance of CYP3A enzymes in the distal gastrointestinal tract led to a "bypass" of the CYP3A-mediated first-pass metabolism and an increase on the intestinal availability (F_G)[1]. The purpose of this work is to explore the implications that the aforementioned formulation-dependent differences in intestinal metabolism can have on drug-drug interactions.

Methods: The PBPK model was expanded to incorporate the different aspects of OXY's metabolism [2]. This model was then used to investigate the interplay between drug release, CYP3A-mediated metabolism and DDIs using OXY as a model drug. Simulations were conducted assuming different OXY formulations of varying release rates covering IR tablets to extended release (ER) formulations (24 h release). The ketoconazole plasma, hepatic and intestinal concentration profiles were simulated in SimCYP v14 using the default ketoconazole model within SimCYP, whereas for the DDI simulations the profiles were combined with the mechanistic model developed for OXY in Matlab 2016a. For each formulation a DDI study was simulated in the presence of a strong CYP3A4 inhibitor (ketoconazole). The ratios (with and without interaction) of AUC, oral bioavailability (F), hepatic availability (F_H) and F_G were then evaluated for each formulation.

Results: The simulations demonstrated that a variation of the release rate from rapid to extended release can reduce the DDI magnitude in the presence of a strong CYP3A4 inhibitor by reducing the fold change in the AUC, from 4.5 fold to almost 2 fold. These results are in line with what has been reported previously for OXY where a change in formulation from IR to OROS reduced the AUC ratio from 3-4 to 2 fold in the presence of ketoconazole [3]. A similar trend was observed for the bioavailability ratio (F ratio), where a decrease was observed by switching from IR to ER formulations, from 2.8 to 1.2 fold. Given that the F_H ratio remained relatively constant between formulations and that the changes in F_G ratio were in line with those of oral bioavailability, this suggests that the decrease in the AUC ratio was mainly due to changes in the intestinal first pass between formulations.

Conclusions: This example highlights the importance that formulations can have when evaluating clinically-relevant DDI involving CYP3A substrates. In addition, given that only the F_G ratios were affected by the change in formulation, this approach can be useful to gain information regarding a compound's F_G when IV data is not available. Nevertheless, extended work needs to be conducted to validate this hypothesis.

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IV-45: *Erik Olofsen* The definition and interpretation of utility functions

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Objectives:

Sheiner and Melmon defined the "Utility" of therapy as "Benefit - Harm" [1]. When Benefit and Harm are dichotomized to "absent" and "present", best interpreted as random, and associated with unity costs, Utility becomes the probability of Benefit minus the probability of Harm.

The "true" costs of benefit and harm are hard to specify objectively, and the difference of probabilities (with unity costs) is hard to interpret, because it itself is not a probability.

Roozekrans et al. defined Utility as the probability of "Benefit And No Harm" [2]. This resembles the "Desirability Index" of Renard et al. [3], taking the probability of Benefit as one desirability function, one minus the probability of Harm as a second desirability function, taking their product (weighted geometric mean with weights one), and assuming that the probabilities of Benefit and Harm are independent.

In the study of Roozekrans et al., Benefit and Harm were dichotomized continuous variables, with thresholds that seem to need careful selection. The Utility could then become a function of - in addition to for example effect-site concentration - two thresholds, effectively decreasing its utility.

The first objective of the present study was to reduce the dimensionality of the utility function by finding a way to handle the selection of the thresholds for dichotomization. The second objective was to compare the characteristics of the original, Roozekrans', and an alternative specification of the Utility Function (UF).

Methods:

Instead of dichotomization, trichotomization was applied, by using the fuzzy logic [4] terms "low", "moderate", and "substantial", where the thresholds for membership still need to be chosen, but are more informative than just "absent" and "present". With two Desirability functions each associated with a fuzzy set of three members, nine fuzzy rules were defined to have output Utility values of "very low", "low", "no", "high" and "very high".

Benefit and Harm were simulated using sigmoid functions with lognormal distributions for the pharmacodynamic parameters C100 and gamma, where C100 is the effect-site concentration giving a 100% increase of effect relative to (an arbitrary) baseline, and gamma a shape parameter. Thresholds for "moderate" and "substantial" were set to 25% and 50%. From N=25000 simulated values, their membership to the fuzzy sets were calculated by the number of times the values were within the threshold ranges (0, 25%, 50%, and infinity) divided by N.

Utilities were studied as a function of effect-site concentration, typical values of C100, gamma, and their (co)variances.

Results:

As judged by visual inspection, the UF proposed here had similar characteristics to the one by Roozekrans et al., with respect to their dependence on the values of the pharmacodynamic parameters underlying the intensity of Benefit and Harm, even though the latter was evaluated with one fixed value for the threshold for Harm.

The effect of a difference between the parameters for Benefit and Harm are the most important for decision making. Findings include: 1) Because the thresholds chosen are below the C100, an increase in gamma moves the UF closer to the C100, so an increase in the gamma of Benefit is likely to give higher values for high utility. 2) A higher (population) uncertainty of the value of C100 moves the UF downward for high utility, and upward for low utility.

Conclusions:

While the term "Fuzzy Utility Function" might be proposed for the one studied here, it might actually give a more crisp interpretation than one with just two thresholds for dichotomization, where it provokes discussion on how these should be chosen. However, this depends on how "easy" it is to define "moderate" and "substantial" Benefit and Harm.

As Renard et al. note, the classical UF can have the value of zero for the entire dose or concentration range. In that case, there can indeed still be a value for the effect-site concentration that gives the highest value of "high" or "very high" utility, even if these are matched by simultaneous highest values of "low" and "very low" utility.

Instead of one classical UF, the present approach gives about four UFs to consider when comparing two drugs. It could be possible that one drug gives higher values for "very high" utility, but even much higher values for "very low" utility; it depends on the application how these should be interpreted.

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IV-46: *Sean Oosterholt* Implications of a model-based dosing algorithm for tacrolimus in paediatric kidney transplantation

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Objectives: Epidemiological data suggests that the global burden of patients with renal failure who receive renal replacement therapy is more than 1.4 million and that this number is growing by 8% a year. Once transplanted kidney survival is roughly estimated as 95% for the first year, 85-90% for 5 years and about 75% survive 10 years. Many factors influence the clinical outcome of kidney graft, such as, whether the kidney is from a living donor, match in terms of blood group and tissue type, graft quality, surgical complications, kidney disease and overall health of the patient receiving the transplant. Most importantly is an adequate immunosuppressive treatment directly following transplantation. Adequate Immunosuppression in a patient depends on various factors, including the choice of immunosuppressant and the dose regimen. This is a problematic area for paediatric patients where information is limited compared to adults and dosing is often empirically based on body weight. This in turn can lead to complications such as overexposure. The aim of the project was to investigate the impact of current dosing and dose adjustment strategies for paediatric patients undergoing kidney transplantation, taking into account the therapeutic target levels and key covariate factors such as age, weight, co-medication, kidney function and donor status.

Methods: Clinical data from 46 paediatric kidney transplant patients (age range: 2-18 years old) were used to retrospectively characterize the pharmacokinetics and investigate the relationship between dose and systemic exposure to tacrolimus. Due to most patients only having trough samples (C_0), individual pharmacokinetic parameters were described using prior information from a previously published PK model [1] with $PRIOR in NONMEM. Tacrolimus dose optimization was then evaluated through 1) clinical trials simulations including different dose adjustment scenarios and 2) comparison of a model-based dosing algorithm with dose adjustment based on therapeutic drug monitoring.

Results: The paediatric data were fitted by a two-compartment model with first order absorption and elimination, with IIV on Ka, V1, CL and Q. Due to the sampling scheme of only trough concentrations none of the parameter estimates changed more than 5% relative to the prior values. Of the investigated covariate effects prednisolone had a positive statistically and clinically significant effect on clearance (Emax model with an ED50 of 35 mg and a maximum increase of clearance of 249%). Additionally, the patients who were prescribed omeprazole had an average decrease in clearance of 10%. Age, haematocrit, donor status and GFR were found to have no significant effect on any of the PK parameters. Dose optimization based on weight bins increased the proportion of patients within the target range (trough concentration between 5-10 ng/ml) after the first dose more than 75% compared to the 0.1 mg/kg recommended dose: <10kg (0.4 mg/kg), 11-20kg (0.2 mg/kg), 21-30kg (0.15 mg/kg), 31-50kg (0.1 mg/kg), 51-60kg (0.08 mg/kg), 61-70kg (0.07 mg/kg), >70kg (0.06 mg/kg). Combining a model-based algorithm with the standard therapeutic drug monitoring allowed for further increase of the number of patients with drug exposure within the target therapeutic range (>99% of the patients).

Conclusion: The use of priors allowed for the characterization of PK parameters and covariate effects in sparsely sampled paediatric data. Subsequent simulations showed possible points of improvement in current practice, such as weight-banded dosing regimen, which greatly increase the probability of achieving

a target therapeutic range. Moreover, unlike current practice, our analysis shows that one does not need to wait for steady state levels to confirm individual exposure if TDM is applied in combination with the proposed model-based dosing algorithm.

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IV-47: *Taniya Paiboonvong* Population Pharmacokinetics of Sitafloxacin in Thai Critically Ill Patients with Pneumonia

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Objectives: Severe pneumonia is one of the most infections among critically ill patients, associated with a high mortality rate. Sitafloxacin is a new fluoroquinolone antimicrobial agent with broad-spectrum activity, including multidrug-resistant organisms. Additionally, sitafloxacin showed a potent in vitro activity against nosocomial respiratory tract pathogens (e.g., Pseudomonas aeruginosa and Acinetobacter baumannii) which are major causes of infection in intensive care unit (ICU) [1, 2]. Sitafloxacin has been approved for oral formulation and used in Thailand for treatment of urinary tract infections and lower respiratory tract infections since 2011. Oral sitafloxacin was rapidly absorbed and has a high bioavailability, including widely distributed into various tissues [3]. According to a population pharmacokinetic (PK) analysis of sitafloxacin in Japanese subjects, changes in covariates could effect on the PK parameters [4]. Thus, physiological changes in critically ill patients may alter the PK of sitafloxacin. The aim of this study was to develop a population PK model for sitafloxacin in Thai critically ill patients with pneumonia.

Methods: Plasma samples were obtained from 12 critically ill patients admitted to ICU, Ramathibodi Hospital, Thailand. Sitafloxacin was given as a 200 mg single dose on fasting stage. Serial blood samples (seven time points) were collected in each patient prior to the first dose of sitafloxacin and at 0.5-2, 3-4, 5-6, and 7-9 hours post dose. Plasma concentrations of sitafloxacin were determined using liquid chromatography–tandem mass spectrometry (LC/MS/MS) assay. The data were analyzed using the nonlinear mixed-effect modelling software (NONMEM) with FOCEI method. One- and two-compartment model were tested to characterize pharmacokinetics and the covariates were screened for their significant impact on the PK parameters. Age, sex, body weight, creatinine clearance (CLCr) estimated by Cockcroft and Gault equation, and acute physiology and chronic health evaluation (APACHE) II score were evaluated as covariates using a stepwise forward selection (α=0.05) and backward elimination (α=0.01). The final PK model was validated using bootstrap analysis.

Results: The median age and weight of the patients were 57 [range 26-75] years and 52 [range 38.5-74.5] kg. Plasma concentrations of sitafloxacin were best described by one-compartment model with first-order absorption. Clearance (CL), volume of distribution (V) and absorption rate constant (Ka) were estimated to be 7.06 L/h, 119 L, and 0.486 h-1, with the interindividual variability (IIV) of 82.2%, 48.3%, and 121.5%, respectively. Age was only a statistically significant covariate on volume of distribution (V = 119 x (age/57)-1.91). Increase in age will lead to a smaller volume of distribution.

Conclusions: The PK profiles of sitafloxacin in Thai critically ill patients were best described by one-compartment model. Volume of distribution of sitafloxacin was influenced by age. The model can be useful to determine an appropriate dosage regimen.

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IV-48: *Kwan Cheol Pak* Physiologically based pharmacokinetic modeling of Herceptin and human pharmacokinetic prediction

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Objectives:

The PBPK approach is known to be superior to traditional allometric approach when it comes to predictability of human PK based on preclinical animal PK experiment[1].

The purposes of the present study were to measure the serial Herceptin concentrations within each mouse by optical imaging after intravenous administration of Herceptin (monoclonal antibody widely used to treat patients with HER-2 receptor positive breast cancer) and construct PBPK models for Herceptin. By doing so, we tried to show the potential utility of nonlinear mixed effect modeling (NONMEM) and optical imaging in pre-clinical PK evaluation.

Furthermore, we also tried to predict the Herceptin concentration changes over time in interstitial fluid of major organs using the PBPK, which could be combined with the models for exposure-biochemical signal network change relationships and ligand-receptor interaction model of Herceptin.

Methods:

PK study was conducted in 24 male Balb/c-nude mice, where serial PK blood samples (0.5, 2, 4, 6, 24 h after intravenous injection of fluorescence-labeled Herceptin) in each mouse were drawn, and the blood concentration was measured by IVIS spectrum optical imaging system.

At 24 h, heart, lung, liver, spleen, and kidney were extracted from mice, and the concentrations of them were measured by IVIS spectrum optical imaging system.

A whole body PBPK (WBPBPK) modeling analysis was constructed based on the known physiological values of mouse including volumes of major organs, blood / lymphatic flows through the organs, and tissue partition coefficients (tissue versus blood) were estimated using NONMEM (version 7.3) subroutine ADVAN13 using first order conditional estimation with INTERACTION method.

Using the WBPBPK model, clinical trial simulation was performed with 1,000 replicates, referencing the human physiological values from literature and a previous clinical trial, in which healthy male subjects received intravenous herceptin at 6 mg/kg over 1.5 hours.

Then the simulated PK data in human was compared with real observed data in the previous study.

Results:

A whole body PBPK model describing the herceptin concentration over time in blood and other major organs in mouse was successfully developed and predicted the concentrations in blood, lung, liver, spleen, kidney and heart well.

A common tissue clearance with its unexplained inter-subject variability was included in the final model, which was estimated to be 0.0118 ml/h. Fraction of lymphatic drainage contributing venous blood concentration of herceptin (FR_L) was estimated to be 0.319. K_p for lung, liver, spleen, kidney, and heart relative to blood were 3.67, 3.56, 1.06, 1.20, and 0.769, respectively.

The predicted mean area under the concentration time curve (AUC), and maximal concentration (C_{max}) were similar to those of observed in a previous clinical trial[2]. The ratios of simulated versus observed AUC and C_{max} were 1.02 and 0.72, respectively.

Using the whole body PBPK model, the mean herceptin concentration over time, and AUC with their 95% prediction interval in various organs in human could be predicted.

Conclusions: We successfully built the WBPBPK models with high human predictability based on mouse experiment with serial PK blood sampling in each mouse by successful implementation of optical imaging. The current study provided the potential synergistic applications of WBPBPK and optical imaging in the prediction of human PK based on the preclinical data in the early stage of drug development process.

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IV-49: *Semra Palic* Exploring dose-dependent pharmacokinetics of miltefosine in pediatric visceral leishmaniasis patients from East Africa

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Objectives:

Miltefosine is currently the only oral drug available for treatment of the neglected tropical parasitic disease visceral leishmaniasis (VL). Conventional 2.5 mg/kg/day dosing of miltefosine was recently shown to be less effective in pediatric VL patients compared to adults in Eastern Africa, and a PKPD relationship between exposure (AUC 191–767 ug*day/mL) and VL relapse was established.[1],[2] Therefore, an open-label clinical trial (LEAP0714) with increased mg/kg miltefosine dosing based on an allometric formula was conducted in pediatric VL patients in Uganda and Kenya. Results of this trial unexpectedly indicated a lower than dose-proportional increase in $AUC_{d0\text{-}28}$. The main objective of the current analysis was to investigate the reasons underlying the observed phenomenon; therefore a pooled analysis of pediatric data with the two different dosing regimens was performed to further characterize observed non-linearities.

Methods:

From the previous LEAP0208 trial 18 pediatric patients (age 7-11) were selected receiving the conventional miltefosine dose of 2.5 mg/kg/day p.o. for 28 days.[2] In LEAP0714, 30 pediatric patients (age 4-11) received miltefosine p.o. based on an allometric dosing formula (equivalent to 2.7 to 3.9 mg/kg/day). Plasma samples were nominally collected on the screening day, during the treatment days 1, 7, 14, 28, and at follow-up period at days 56 and 210, while in LEAP0714 a sample on day 21 was also collected. A total of 325 miltefosine plasma concentrations were analyzed by liquid chromatography tandem mass spectrometry. Data were analyzed in a population approach using the first-order conditional estimation with interaction (FOCE+I) in NONMEM (version 7.3.0, Globomax, USA) using Pirana as interface (version 2.9.6). Both total amount miltefosine mg/day (AMTT) and cumulative mg/kg/day dose (CD) were explored as a covariate on PK parameters using various parameterizations.

Results:

The previously developed two-compartmental PK model with first-order absorption and elimination showed overprediction of miltefosine accumulation in the last week of treatment for the allometric dose PK data.[2] Similar to the previous model developed on the 2.5 mg/kg data, a lower bioavailability (F) of -68.6% (RSE 8%) in the first treatment week was required (**Δ**OFV -19.4), presumably due to initial malnourishment and malabsorption. This decrease in F appeared highly variable between subjects (BSV 83.9%, RSE 10%, **Δ**OFV -223.9). AMTT and CD were additionally tested as covariate on all PK parameters to explain observed non-linearities in the later part of the treatment and CD? was found to have the most impact again on F. A piece-wise linear function best fitted the data, where a CD higher than 25 mg/kg decreased F by 3.5% (RSE 13%) for every 5 mg/kg increase (**Δ**OFV -17.2). Residual variability was described by a proportional error of 32.7% (RSE 11%). Model predicted individual PK profiles were used to estimate individual miltefosine exposures. In the first week of treatment median $AUC_{d0\text{-}7}$ was 8.56µg*ml/day (range

0.53 to 28.6) and 20.5µg*ml/day (range 4.1 to 95.1), for the linear and allometric dosing regimen, respectively; while the median AUC_{d0-28} was 322.1 (range 263.7.6- 472.3) µg*ml/day and 361.9 (range 206.1- 627.1) µg*ml/day, respectively. Despite these nonlinearities, the increased exposure in the first part of the treatment following the allometric dosing regimen might have contributed to the observed efficacy for this regimen.

Conclusions:

The results indicate that miltefosine F is dose-dependent, with two separate non-linearities observed: a decrease in F at the start of treatment independent of dose and an effect of CD on F in the later phase of treatment. The latter effect might possibly be explained by slow accumulation of miltefosine in the gastrointestinal membrane cells and subsequent dose-dependent saturation of paracellular transport, corroborated by the extremely slow absorption rate of miltefosine.

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IV-50: *Shan Pan* Efficacy and toxicity of intravenous salbutamol in children with acute severe asthma: a prospective clinical PKPD study

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Objectives: Salbutamol is a short-acting selective beta-2 adrenoceptor agonist for treating asthma in adults and children. Intravenous salbutamol (IVS) is routinely used as second line treatment for childhood acute severe asthma as per the British Thoracic Society (BTS). IVS doses in children are extrapolated from adults based on body weight, and no maximum dose in children has been recommended while children may receive doses far greater than the maximum adult dose. Our study aimed to develop new rational dosing guidelines for IVS in children through exploring relationships between IVS blood concentrations and efficacy and toxicity measurements in children with acute severe asthma.

Methods: A prospective Phase II study was conducted in Emergency Departments (EDs) and Paediatric Intensive Care Units (PICUs) across London, UK (EudraCT No. 2014-002996-27). Children with acute severe asthma were recruited from two distinct cohorts: the ED cohort and the Children's Acute Transport Service (CATS) cohort. In the latter case, children were taken to PICUs.

Plasma concentrations, efficacy and toxicity measurements were available from children receiving IVS with intermittent nebulised doses. Asthma severity was measured by the three-item composite score Paediatric Asthma Severity Score (PASS) [1]. Toxicity-associated physiological measurements were collected from blood gas, blood glucose and cardiovascular tests. In total eight individual toxicity measures were examined in the current study.

One- and two-compartment PK models were tested for the time course of salbutamol plasma concentrations after IVS. Plasma concentrations at baseline were estimated due to long and uncertain pre-treatment history of salbutamol. PASS (re-categorised into three) and the individual items (each with three categories) were assessed by ordered logistic regression considering time-varying plasma concentrations. For toxicity measures, a hypothetical effect compartment was added to examine whether delayed onset in toxicity effects occurred after IVS.

Correlation analysis was conducted between predicted plasma concentrations and observed toxicity measurements, and between predicted and observed toxicity measurements.

Data manipulation and graphical analysis were conducted in R (version 3.4.3). IVS PKPD model development was performed in NONMEM® (version 7.3).

Results: In the current study, data were available from 47 children aged between 1 and 15, with 165 plasma samples, 102 PASS measurements, and 178-245 measurements for each toxicity measure.

A one-compartment PK model well described the time course of salbutamol plasma concentrations after nebulised and intravenous salbutamol doses. Body weight, added allometrically, was found as a statistically significant covariate. The covariate effect of age was not found significant through maturation function.

For PASS and the individual items, the addition of linear concentration-efficacy relationship didn't significantly reduce objective function value (OBJV), except for work of breathing. Emax concentration-efficacy relationship, however, significantly reduced OBJV based on likelihood ratio test or Akaike information criterion (AIC), with reported EC50 values ranging between 0.2 ng/mL and 0.5 ng/mL.

Correlations between plasma concentrations and toxicity measurements were not found significant, and sigmoidal Emax concentration-toxicity relationships significantly improved the correlation coefficient for all. Toxic effects increased immediately with the increase of plasma concentrations, the opposite for pH and base excess measures; these findings were consistent with physiological observations. EC50 values were estimated between 28 ng/mL and 360 ng/mL.

Conclusions: The current study explored PKPD relationships for efficacy and toxicity measurements after IVS. Based on the PKPD relationships, future investigation concerning clinically significant changes is required to determine maximum IVS dose in children with acute severe asthma.

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IV-51: *Alice Panchaud* Prediction of escitalopram exposure in infants through breastfeeding by modeling and simulation

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Objectives: Worldwide about 10% of pregnant women and women who have just given birth experience a mental disorder, primarily depression. If left untreated, depression have been associated with adverse outcomes for the mother, the infant and their family environment, such as reduced maternal sensitivity and involvement in caregiving, and child emotional or behavioral difficulties. Escitalopram figures among the most frequently prescribed drugs for the treatment of depression in pregnant and breastfeeding women. Available information on exposure to escitalopram during the perinatal period and its excretion into breast milk is based on heterogeneous and incomplete data. The aim of the study was to better characterize the exposure to escitalopram and its metabolite in maternal blood and breast milk. The model was used to quantify the potential risks associated with the use of this medication during breastfeeding.

Methods: The study population was composed of women taking escitalopram or racemic citalopram stemming from a multicenter prospective cohort study enrolling pregnant women under treatment with serotonin reuptake inhibitors (SSRI) and willing to breastfeed. First, a structural model was built for escitalopram (SCIT) in plasma using a one compartment model with first order absorption and elimination in NONMEM®. Then, drug breast milk concentrations were added to the basic model and described by estimating milk-to-plasma ratios (MPR). The effect of different influential covariates such as age, bodyweight, CYP2C19, 2D6 and 3A4/5 genotypes (categorized according to the phenotypic activity) or milk fat content and time after delivery on drug pharmacokinetics was tested. Finally, drug exposure of a suckling child through breast milk was predicted by simulating 5'000 mother-infants pairs under various conditions of maternal characteristics and milk consumption (11±3 feedings per day range 6 and 18 times/day, assuming a typical milk volume of 150 mg/kg/day). The relative infant dose (RID), that is equivalent to the ratio of drug dose ingested by an exclusively breastfed infant with the weight-adjusted maternal dose, was calculated for each mother-infant pair.

Results: The study enrolled 33 patients under escitalopram or racemic citalopram who provided 80 blood and 104 milk samples. Mean SCIT clearance was 32.3 L/h with a between-subject variability (CV%) of 31% and an apparent volume of distribution of 1590 L. Poor metabolizers of CYP2C19 showed a significant 51% decrease in SCIT clearance compared to the other genetic groups. The other genetic polymorphisms did not show any influence on SCIT or SDCIT pharmacokinetics. SCIT was characterized by a MPR of 1.9, while an increased milk fat content was significantly associated with an increased drug transfer into breast milk (+28% for SCIT when fat amount doubled from 3.1 to 6.2 g/100 ml). Drug concentrations was slightly higher 1 month after delivery than compared to labor/early postpartum. Simulations suggest that the average RID of an exclusively breastfed infant after 10 mg escitalopram is 3.5% (from 0.8% to 12.7%). RID would increase mostly in mothers who are PM for CYP2C19 but remained low (average RID 6% from 3% to 17 %).

Conclusions: Escitalopram showed moderate between-subject variability in blood concentrations, partially explained by genetic polymorphisms in CYP2C19. Milk concentrations were similarly variable and mainly

influenced by the milk fat content in addition to genetic polymorphism. The limited exposure to escitalopram through breast milk, as expected based on previous incomplete data, could be confirmed. These findings provide reassurance with a good level of certainty for clinicians and pregnant women successfully treated with escitalopram or racemic citalopram.

IV-52: *Navarat Panjasawatwong* Population pharmacokinetics of rifampicin in Vietnamese Children with Tuberculous Meningitis

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Introduction/Objective: Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis (TB), characterized by the presence of tuberculosis bacteria in the brain parenchyma. Due to the relatively weak immune system in children, they more commonly contract TBM compared to adults. The drug regimens used today to treat TBM in children have been extrapolated from the current treatment of pulmonary TB in adults. The usefulness of this approach has been challenged by several studies showing that the drug exposure to the four first-line anti-TB drugs (i.e. isoniazid, rifampicin, pyrazinamide and ethambutol) after a standard treatment were lower in children compared to adults.

Rifampicin is the backbone of the first-line anti-TB combination treatment today. However, the penetration of rifampicin into cerebrospinal fluid (CSF) is poor. There is limited information on the pharmacokinetics of rifampicin in children with TB, especially in children with TBM. The objective of the study was to investigate the population PK of rifampicin in Vietnamese children with TBM.

Methods: One-hundred Vietnamese children with TBM were treated with an 8-month pediatric anti-TB treatment regimen which was based on the 2006 World Health Organization guidelines. The treatment consisted of isoniazid (5 mg/kg), rifampicin (10 mg/kg) and ethambutol (15 mg/kg) for 8 months, with the addition of pyrazinamide (25 mg/kg) for the first 3 months and streptomycin (15 mg/kg) for the first 2 months. The drugs were given once daily.

For each child, two plasma samples were collected on days 1 and 14 after the first dose. One plasma and one CSF samples were drawn less than 15 minutes apart on days 30 and 90. The concentrations of the four drugs were quantified using a fully validated liquid chromatography-tandem mass spectrometry method.

Pharmacokinetic properties of rifampicin in plasma and CSF were evaluated using nonlinear mixed-effects modelling in NONMEM version 7.4. First-order conditional estimation method with interaction (FOCE-I) was used throughout the model-building process. Different structural, variability and covariate models were evaluated. Enzyme maturation and enzyme turnover models were also evaluated.

Results: Fifty-six percent (56%) of the patients were male and the median age was 3 years (IQR: 1-7). A total of 492 plasma and 154 CSF concentrations from 100 participants were included in the model. Rifampicin concentration-time data were best described by a one compartment disposition model with transit absorption (one fixed transit compartment). Inter-occasion variability was added on elimination clearance, volume of distribution and mean transit time. An enzyme turnover model was retained in the final model to describe the autoinduction of rifampicin, resulting in an enzyme induction half-life similar to what have been seen previously. A CSF compartment was integrated into the final structural model to describe the distribution of rifampicin into the brain. The distribution of rifampicin into CSF was assumed to be passive and governed by a first-order rate constant.

Body weight and age were significant covariates in the final model. Body weights were implemented as a fixed allometric function on elimination clearance and volume of distribution. Ages were included as a

maturation factor on elimination clearance to describe the maturation of enzymes during the early years of life.

Conclusions: The population pharmacokinetics of rifampicin were well explained by a one-compartment distribution model with one-fixed transit compartment in the absorption phase. The exposure to rifampicin was higher on day 1 compared to day 14 and was described in the model by an enzyme autoinduction. The developed model can be used to optimize the dosing of rifampicin to achieve adequate exposure in CSF.

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IV-53: *Christophe Passot* Therapeutic drug monitoring of eculizumab in atypical hemolytic uremic syndrome

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Objectives:

Eculizumab is a monoclonal antibody toward C5 fraction of the complement system. It is approved to treat atypical hemolytic uremic syndrome (aHUS), an orphan disease, at a fixed dose of 1200 mg every 2 weeks. It has been demonstrated that a serum concentration of 99 mg/L is sufficient to suppress complement activity [1]. A pilot study revealed that serum trough concentrations were excessively high in many patients and that administration schedule may be individualized [2]. This prospective multicenter study aimed at (i) quantifying pharmacokinetic variability of eculizumab in aHUS patients and (ii) to design a Bayesian model for individual dosing adjustment of eculizumab.

Methods:

This work is a two-step study. The first part was conducted on 40 patients with aHUS from 6 hospitals. Eculizumab trough concentrations were determined on blood samples drawn in 2016 with a validated ELISA assay [3]. A population PK model was made using Monolix 4.3.3 software (Lixoft, Orsay, France). Body weight, height, sex and age were tested as covariates on PK parameters. Individual time since last dose to reach 100 mg/L steady-state trough concentration (TLD_{100}) was computed for each patient. Patients whose theoretical individual administration interval was at least 21 days were selected for dose tapering. The second part consisted in the development and validation of a Bayesian model for dosing adjustment of eculizumab based on samples drawn in 2017 from patients with TLD_{100}>21 days. Bayesian model used structural, interindividual, residual and covariate model parameters estimated during the first part, as prior information. Individual PK parameters assessed with the Bayesian model were used to predict eculizumab trough concentrations after interval lengthening. Predicted concentrations were then compared with observed concentrations after lenghtening.

Results:

During the first part, a total of 170 eculizumab serum trough concentrations were available in the 40 eligible patients. Eculizumab was administered every 2 weeks in 37 (92.5%) patients out of 40 patients of the first step (92.5%) and every 3 weeks in 3 patients (7.5%). A median of 4 blood samples were available for each patient (range: 2-5). The mean individual eculizumab trough concentration was 476.1 mg/L (range: 124.3-1064.6 mg/L) Eculizumab pharmacokinetics was best described using a one-compartment model with first order elimination rate constant. Population volume of distribution and clearance were 3.1 L and 0.13 L/day, respectively. Body weight increased significantly elimination clearance (b_{WT_CL}=1.16, p=0.0001). TLD100 was >21 days in 37 patients (92.5%). In 13 out of these 37 patients, individual PK parameters were assessed with the Bayesian model. Eculizumab trough concentrations after dose tapering were predicted

and compared with observed concentrations. The correlation coefficient of observed vs predicted eculizumab concentrations was 0.92, with a mean of absolute bias of 47.2 mg/L.

Conclusions:

In this ongoing work, we confirmed that eculizumab administration could be individualized through therapeutic drug monitoring. The estimation of PK parameters in a relatively large cohort for this orphan disease allowed to construct a Bayesian model. This model allowed a satisfying prediction of eculizumab trough concentrations after interval lengthening. It is currently in use to determine PK parameters of eculizumab in newly enrolled patients and to determine if administration lengthening can be performed.

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IV-54: *Dimple Patel* Using real world data to assess SGLT2 Inhibitor cardiovascular benefit and impacts of patient population characteristics

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Objectives: Following a successful cardiovascular (CV) outcome study EMPA-REG (1), SGLT2 inhibitor (SGLT2i) empagliflozin was approved for reducing the risk of cardiovascular death in adults with T2DM and established cardiovascular disease. AstraZeneca's CVD-REAL study showed SGLT-2i, as a class, significantly reduced death and hospitalisations for heart failure versus other type-2 diabetes (T2DM) medicines using real world evidence data (2). We analyzed two real world data: an Electronic medical record (EMR) and a Claim database to assess SGLT2i CV benefit compared to other T2DM medications (standard of care or SOC). We explored the impacts of patient characteristics, such as baseline CV risk and renal status, on the CV benefit. The results can be applied to leverage real world data, assess effectiveness of an approved drug and inform the clinical trial design for a new drug.

Methods: Quintiles/GE EMR (1995-2016) contains sparse patient-level data and prescriptions may or may not be filled, however also contains large number of laboratory data. Truven database (2008-2016) contains longitudinal patient-level claim data from inpatient as well as outpatient and facility settings, but limited laboratory data. T2DM patients with at least one SGLT2i prescription, without any SGLT2i prescription but 1 recorded activity in (GE EMR) and without any SGLT2i but other new antidiabetic medication prescription (Truven) in the time period were included. A one-to-one propensity score method was applied to select non-SGLT2i patients (SOC) to match SGLT2i patients' baseline characteristics. CV endpoints of interest included MI, stroke, CV death (MACE), and hospitalization due to heart failure (HHF). Three patient populations for all patients, patients with prior CV risk (with any prior CAD, CD, PVD or events of interest), and patients with prior CV risk/renal impairment were analyzed. ICD 9 and ICD 10 codes were used to search for type 2 and CV events. Prxmatch search function and NDC codes were used to search for SGLT2 drugs. First SGLT2i date, non SGLT2i selected activity date (GM EMR) and the new non SGLT2 first prescription (Truven) in the time period were used as the real world evidence study start date. Time to first CV event (MACE or MACE + heart failure (HF)) was analyzed using the COX proportional hazards model. The CV treatment differences between SGLT2i and SOC were presented for all 3 populations.

Results: For GE EMR and Truven Claim, more than 70,000 and ~200,000 T2DM patients on SGLT2i and the same number matched SOC patients were included. For GE EMR, baseline variables age, sex, diabetes duration, race, HbA1c, eGFR, prior CV risk, BMI, SBP/DBP, LDL/HDL, etc. were included in the propensity score matching. For Truven Claim, only limited baseline variables such as age, sex, diabetes duration and prior CV risk were included in the matching due to the database limitation. For GE EMR, stroke, MI and HF only were analyzed since no death or consistent hospitalization information was available. For CV endpoints of stroke + MI and stroke + MI + HF, statistically signification CV risk reductions ~ 10% to 20% for SGLT2i versus SOC were observed with HF risk reduction having a larger effect size in all patient population. For prior CV risk population, a similar trend was observed without statistical significance. For prior CV risk and moderate renal impairment (baseline eGFR ≤ 60 mL/min/1.73 m2) population, the sample size was too small to conclude. For Truven, deaths in circulation system were used instead of CV death and CKD status was used for renal impairment due to lack of eGFR data. HFs were analyzed to keep the consistency with EMR data, even though hospitalization information is available. Consistent treatment benefits were observed for both MACE and MACT+HF endpoints for all 3 populations.

Conclusions: Though there are issues in real-world data collection such as lack of quality and content, the real world data can contribute in evaluating patients' characteristics, treatment effects and population characteristic's impact. The results can be used to inform the clinical study design for a similar treatment. Due the differences between the real world and clinical data, relative effect magnitudes not the exact effect sizes should be referenced and further researches are needed to account for potential bias and confounding.

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IV-55: *Henning Schmidt* Reproducible submission-ready Word reports based on open source tools

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Introduction: Pharmacometric reports typically contain a large number of figures, tables, text files, in-line text, and numerical values that have been generated during the conduct of analyses. While these results are often generated in a script-based manner, reporting of these results is complicated by corporate requirements to use Microsoft Word and a specific in house-style guide, requiring scientists to copy, paste, and format results manually in a time-consuming and error-prone process.

Wilkins and Jonsson [1] presented an approach to Reproducible Pharmacometrics that allowed a full end-to-end scripting of the analysis and the creation of publication-ready reports. Their solution was based on LaTeX [2], knitr [3], and R [4]. While this approach is very powerful, LaTeX can be perceived as a cumbersome language. More importantly, the output is a PDF rather than a Word document, which often does not comply with corporate publication policy. In recent years, R Markdown [5] has been developed, allowing to use the more lightweight language Markdown, and RStudio [6] supporting the conversion to Word. However, no R Markdown support is available for critical Word features, such as cross-references, figure and table captions, and choice of more complex Word styles, impeding the generation of submission-ready Word documents.

In this poster, a Markdown based framework is presented that leverages open source tools to allow the creation of submission-ready Word reports, using any desired Word style, and to automatically integrate analysis results without the need for manual copy and paste.

Methods: The development of the reporting framework requires the combination of several elements. One of the most important elements is the definition of a language to be used to write the report. Markdown [7] was selected as a basis and its syntax was extended with additional elements, such as tags for page breaks, landscape and portrait mode, definition of figures and tables and related captions and legends, cross references. The conversion of Markdown to Word DOCX is performed by Pandoc [8]. Before the extended Markdown syntax can be processed by Pandoc, the extended Markdown and the figures and tables need to be pre-processed and the extended Markdown converted to normal Markdown. Figure post-processing is done using Ghostscript [9] and ImageMagick [10] and involves scaling, cropping, and conversion from PDF files to a format suitable for import into Word. After Pandoc conversion of the Markdown document, the resulting Word document needs to be post-processed to ensure the use of the correct style across the final Word report. The mapping of styles to report elements is defined in a template settings file. Simple interface functions were developed for R and other scripting environments, allowing to export matrices, tables, and data frames into a text-based format that serves as container for tables to be imported to Word and to execute the framework on a user provided extended Markdown document. In addition, these interfaces generate information that allows to link the report elements to the scripts and outputs that were generated during the analysis, leading to full traceability.

Results: The resulting Markdown based framework has been applied in the creation of several Word reports for submissions to Health Authorities. Its user-friendliness has been greatly improved by employing the text editor Notepad++ [11], allowing syntax highlighting for the extended Markdown language and a customizable context menu that appears on the right click of the mouse. This context menu allows to

include often used report text and (extended) Markdown elements into the report document and thus speeds up report writing and learning of the syntax.

Conclusions: The approach uses existing technology that is not particularly difficult but does require some custom scripting to link different tools. This scripting, however, does not need to be performed by the end-user. The work demonstrates that increased accuracy, efficiency, credibility, elimination of transcription errors, traceability, reproducibility, including the resulting Word report, is possible.

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IV-56: *Violeta Balbas-Martinez* Physiologically-Based Pharmacokinetic model for Ciprofloxacin in healthy children and approximation to children with complicated Urinary Tract Infection

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Objectives:

Ciprofloxacin is a second generation fluoroquinolone with a broad antibacterial spectrum labelled for treatment of complicated urinary tract infection (cUTI) in children. In a recent population pharmacokinetic study of ciprofloxacin administered to children suffering from cUTI, it was demonstrated that in this patient population, the apparent volume of distribution (V) and total plasma clearance (CL) showed up to a 83.6 and 41.5% decrease compared to healthy children[1].

The goal of the present study was to (i) build and evaluate a ciprofloxacin PBPK model for the adult population, (ii) extrapolate the adult model to the healthy paediatric population, (iii) perform a sensitivity analysis to identify those factors most important for describing elimination and disposition, and (iv) adapt the PBPK model in healthy children to the paediatric population suffering from cUTI.

Methods:

PK-Sim® (Open-Systems-Pharmacology.com) was the PBPK software and the well-established workflow for PBPK model development in children [2] was followed.

First, a ciprofloxacin adult PBPK model was developed with data extracted from literature[3–8] after intravenous and oral administration. Ciprofloxacin exhibits (i) renal elimination mediated by glomerular filtration (GFR) and tubular secretion (TS_CL_{int}), (ii) CYP1A2 mediated metabolism (CL_{CYP1A2}), and (iii) biliary excretion (CL_{Bil}). A value of 1.25 ml/min/kg corresponding to 15% of the adult CL was used for $CL_{Bil.}$ An apical efflux transporter was added to fully characterize renal elimination. Distribution was characterized using tissue-to-plasma partition coefficients predicted by the *in silico* tissue composition approach proposed by Rodgers et al.[9] and the standard PK-Sim® model for small molecules. With respect to absorption, dissolution profiles were described by the Weibull function. Afterwards, assuming linear pharmacokinetics, TS_CL_{int}, CL_{CYP1A2} and transcellular intestinal permeability were optimized.

Second, age-dependent physiological and anatomical changes were implemented enabling paediatric predictions from the PBPK model established for adults. PBPK based predictions were challenged with plasma concentrations simulated from a population pharmacokinetic model developed with data from 150 children (3 month to 17 years) of whom 97% had normal renal function or mild renal impairment[10].

Third, a sensitivity analysis was performed to assess the impact of model parameters on the CL and V. An increase of 10% of every model parameter was evaluated. Parameters with sensitivity values < -0.25 or > 0.25 were reported for V and CL.

Finally, to account for the renal impairment in cUTI children, TS_CL_{int} and CL_{CYP1A2} were corrected according to their Kidney Function (KF) computed based on individual cystatin C and creatinine values from a clinical study with 22 enrolled cUTI children[11].

Results:

A PBPK model for ciprofloxacin has been successfully developed for adult and healthy paediatric populations. The model was able to describe ciprofloxacin concentration-time profiles and fraction excreted unchanged in urine (f_e) in close agreement with the observed data. The final estimates obtained for intestinal permeability, CL_{CYP1A2}, and TS_CL_{int} were 3 x 10^{-6} cm/min, 20.61 mL/min and 1.32 L/min/kg tissue, respectively.

The sensitivity analysis revealed that V was greatly affected by tissue internal pH, fraction unbound in plasma and kidney volume, whereas for CL, the contribution of the tubular secretion, together with kidney volume and fraction unbound in plasma were the most influential parameters.

A significant improvement in the prediction of plasma concentrations of ciprofloxacin and f_e were obtained in cUTI patients once TS_CL_{int} and CL_{CYP1A2} were corrected according to the individual values of KF.

Conclusions:

A ciprofloxacin PBPK model has been developed for adult and paediatric populations. Changes in TS_CL_{int} and CL_{CYP1A2} according to KF explained in part the differences seen in the plasma drug concentrations vs time profiles and f_e between healthy and cUTI children. Furthermore, a sensitivity analysis indicated that intracellular pH had a great impact on drug distribution. Interestingly, metabolic acidosis is a common complication of chronic kidney disease[12], which might play a relevant role in the pharmacokinetics of the cUTI population.

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IV-57: *Cesar Pichardo* QSP Modelling of Neurodegenerative Chronic Diseases and Brain Biomarkers: Adding the Effect of Ageing on Brain Volume

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Introduction:

Physiological modelling and simulation including brain physiology (and/or pharmacology) have been typically based on the assumption that brain is a constant volume. However, several studies have shown that the volume of the brain is not constant during the life of a person, being fully developed around 20 years and starting to decrease after this age [1]. When studying neurodegenerative chronic diseases, e.g. Alzheimer's disease, changes in brain volume, either growth during brain development or decrease during adulthood and later ages, becomes quite important in the estimation of the concentration of specific biomarkers in brain, e.g. amyloid beta, cholesterol, etc.

Objectives:

- Developing a new Quantitative Systems Pharmacology (QSP) modelling methodology considering brain volume changes for the estimation of biomarker concentrations.
- Comparing the results of a model with variable brain volume with a model using constant volume.
- Evaluating the effect of the variability of brain volume changes in a given population on the estimation of biomarker concentrations.

Methods:

The methodology proposed includes the implementation of a Quantitative Systems Pharmacology (QSP) model describing the main mechanisms related to Amyloid Precursor Protein (APP) processing and amyloid-beta production and accumulation in brain [2,3] in combination with an "ageing" model considering the effects of ageing on the variations (i.e. decrease) in the brain volume. The model was implemented in Matlab/Simbiology version 2017b (The Mathworks Inc., Natick, USA) as the flexibility of this modelling software allows the modeller adding the additional feature of variable volume in an easy and user-friendly way. The model was simulated using a stiff ODE (ordinary differential equation) solver (ode15s) given the different time scales needed to be considered and the time span being simulated (several decades of a patient live). To evaluate the variability of brain volume changes in a given population, the model was evaluated for three different virtual populations, i.e. only male, only female and mixed (50% males and 50% females) populations, simulating the dynamic biomarker changes for each of them.

Results:

The integrated Quantitative Systems Pharmacology (QSP) model shows sensible simulation results when comparing with clinical data published in the literature. When studying the accumulation of specific biomarkers (e.g. amyloid-beta), using a dynamic model which considers the lifespan of a patient and his brain volume change because of ageing, allows seeing how the decrease in brain volume can be related to the increasing concentration levels observed in the clinic.

Conclusions:

Simulation results from the integrated Quantitative Systems Pharmacology (QSP) model proposed suggest that the inclusion of a variable brain volume can help to have a better dynamic description of neurodegenerative chronic diseases in ageing populations and also to have a better estimation of biomarker concentration levels in this specific tissue.

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IV-58: *Philippe Pierrillas* PKPD modelling of EYP001a (a novel FXR agonist) in healthy volunteers and Hepatitis B patients

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Objectives:

EYP001a is an agonist of the nuclear farnesoid X receptor (FXR) which binds bile acids. FXR agonists, originally discovered for a therapy of non-alcoholic steato-hepatitis, primary biliary cholangitis and metabolic syndrome, were found to have anti-viral activity on Hepatitis B virus (HBV) [1].
The objective of this analysis was to develop a population Pharmacokinetic-Pharmacodynamic model (PK-PD) using biomarker data to assess the influence of EYP001a on FXR pathway in both healthy volunteers and HBV infected patients.

Methods:

Data from two phase 1 studies (including a 4-arm cross-over study to evaluate the impact of food intake and a potential nycthemeral rhythm) conducted in healthy volunteers and HBV-infected patients were included in this analysis. Plasma samples from 91 individuals after single and repeated administrations of EYP001a at 7 different dose levels (from 30 to 800mg) and placebo were analysed for EYP001a and FGF19 concentrations (i.e. fibroblast growth factor 19, the intestinal protein leading to transcriptional repression of the cholesterol 7 alpha-hydroxylase (CYP7A1) and consequently reduced bile salt synthesis and whose transcription is stimulated by FXR receptor). A covariate analysis, using a stepwise approach, was performed to assess the impact of food effect, age, sex, weight-derived covariates (i.e. body mass index…) and also to investigate the potential differences between healthy volunteers and HBV infected patients. Parameters were estimated with the First-Order Conditional Estimation method with Interaction (FOCE-I method) implemented in NONMEM 7.3 (ICON) and model development was guided by residual- and simulation-based diagnostics.

Results:

Plasma pharmacokinetics of EYP001 was best described with a 2-compartment model and an absorption phase modelled using 5 transit compartments. Bioavailability appeared to decrease after repeated administrations and to decrease as dose increases. A lower clearance was found in HBV infected patients (~25%) compared to healthy volunteers, and administration of EYP001a under fed condition decreased the absorption rate by a 2-fold factor but with a similar exposure.
FGF19 time-course in the placebo arm was modelled using a turn-over model and a Kinetic-Pharmacodynamic (K-PD) approach [2] was used to describe the increase of FGF19 production induced by meal intake. EYP001 drug effect was best described using an effect compartment [3] and a steep sigmoidal function (coefficient of sigmoïdicity>2) on the FGF19 production. No difference between HBV infected patients and healthy volunteers was detected for the pharmacodynamic part.
Model evaluation by goodness-of-fit and Visual Predictive Check, were satisfactory.

Conclusions:

EYP001a and FGF19 concentrations were adequately described by the proposed approach and confirm the impact of EYP001a on FXR pathway. This model will be expanded to other biomarkers, such as C4 concentrations (intermediate in the synthesis of bile acids from cholesterol located in the liver) and biliary acids, as they will be available.

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IV-59: *Etienne Pigeolet* Modeling of amyloid accumulation in subjects at risk of Alzheimer's disease under BACE inhibition treatment.

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Objectives: The main pathophysiological hypothesis for the development of Alzheimer's disease currently identifies two abnormal structures suspected to damage neurons in the brain: amyloid beta (Ab) plaques and tangles of tau protein fibers. Several beta amyloid cleaving enzyme (BACE) inhibitors, inhibiting the production of Ab peptides are currently under clinical development.

The pathological time course of biomarkers and clinical symptoms has been characterized [1] indicating that treatments targeting Ab should be administered well before the clinical diagnosis of dementia to have a chance of success.

The slow progression of Alzheimer's disease prevents rapid assessment of treatment efficacy with the cognitive clinical end-points or amyloid plaque imaging techniques. For treatments aimed at reducing the production of Ab, target engagement is easily measured through Ab CSF concentrations. However, the impact of the Ab reduction on the long term progression of amyloid plaques in the brain is unknown.

The aim of this analysis was to assess, through a systems biology/pharmacology model, what level of BACE inhibition is needed in the long run to stop or slow down the amyloid plaque build-up in the brain.

Methods:

The work was started from an existing model [2]. This system biology model consists of modules describing the synthesis and processing of amyloid precursor protein to Ab species, the distribution of Ab species between biological compartments, their aggregation process and the long term progression of soluble and insoluble Ab. This model was built in a stepwise manner: first from mouse data, scaled up to healthy human subjects with validation using monkey data and then extended to AD patients. It is based on the data and analyses from 73 published references.

Further model development was performed for this research: the mouse model was recalibrated in light of latest literature data on some existing processes and from BACE inhibitors. In house PKPD data from phase I studies with CNP520 and other BACE inhibitors published data were added to calibrate a human model.

Model evaluation was performed through various approaches: identifiability was assessed by log-likelihood profiling, inter-parameter correlations and re-estimations by fixing one parameter at a time. Uncertainty was assessed essentially through model variants exploration. The model was also evaluated through its ability to predict data not used for model calibration.

The model was developed with the DBSolve Optimum software (InSysBio, version 36) with fits performed by the DBSolve Maximum Likelihood Estimation method.

Results:

Seven models variants were selected based on different assumptions and goodness of fit. Variations were applied to processes such as synthesis of Ab, destruction of insoluble forms, polymerization, age-dependent changes, presence of Ab42 feedback on Amyloid Precursor Protein production. Two of these variants were further selected for their good fit on the different type of data and for representing model uncertainty. These two models reproduced reasonably well the concentrations of the various amyloid species in plasma and in CSF as well as insoluble forms in brain for healthy subjects and Alzheimer's patients. They were also reproducing reasonably well the same amyloid species in CSF after BACE inhibitor treatments. Some discrepancies with actual data were however observed: the decrease of Ab42 in CSF between healthy subjects and Alzheimer's patients for example was estimated at about 90% by the model while the actual data indicate a decrease of about 50%.

To answer to the research question, simulations were performed with 0, 30, 50 and 80% of BACE inhibition for 10 years starting at 65 or 75 years of age. These simulations predicted that the insoluble Ab42 in the brain would reach about 500 to 1100 % or about 65 to 140% of baseline after 10 years of 80% BACE inhibition when started at 65 or 75 years of age respectively. Comparing to a placebo group, differences would be about -70 and -60% respectively.

Conclusions:

The results hint to a monotonic slow down of brain insoluble amyloid with increased level of BACE inhibition. Given the underlying assumptions and uncertainty of the model, validation of this prediction warrants further studies.

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IV-60: *Nikhil Pillai* Estimating parameters of chaotic systems: chaos synchronization combined with Nelder-Mead search

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Objectives: Deterministic chaos is a prominent feature of many biological systems. We compare an adaptive chaos synchronization (ACS) [1] method with an Extended Least Squares (ELS) method. We highlight challenges for the ELS method when experimental data are sparse and noisy and demonstrate advantages of ACS using the well-known Kirschner-Panetta (KP) tumor model of IL-2 immunotherapy, for which we explore steady states without treatment terms. The governing differential equations of the KP model are provided below.

dE/dT = c*T - mu2*E + p1*E*IL/(g1+IL) + s1 (1)
dT/dt = r2*(1-b*T)*T - a*E*T/(g2+T) (2)
dIL/dt = p2*E*T/(g3+T) -mu3*IL +s2 (3)

with initial conditions $E(0)=E_0$, $T(0)=T_0$ and $IL(0)=IL_0$, where *E*, *T* and *IL* denote the concentration of effector cells, tumor cells and IL-2 cells respectively. Here, c denotes the antigenicity of the tumor, the term p1*E*IL/(g1+IL) models the stimulation of effector cells by IL-2, *s1* represents the external source of effector cells (treatment term), r2*(1-b*T)*T represents the (logistic) growth of tumor cells, *a* denotes the loss of tumor cells by interactions with the immune system, p2*E*T/(g3+T) models the stimulation of IL-2 by the effector cells, mu3 denotes the IL-2 degradation rate, and finally *s2* denotes an additional treatment term for the external input of IL-2 [2]. As in [2], we explore the steady states without the treatment terms thus, in what follows, we set *s1*=*s2*=0.

Methods: We analyzed the structural identifiability of the K-P model using the GenSSI software [3]. We applied ACS to track the system and estimate parameters that enter in a linear fashion, while using Nelder-Mead search to estimate parameters that enter in a nonlinear fashion, the objective function as Root Mean Square Error (RMSE) between the observed and predicted concentrations. We compared the performance of the ACS to the ELS method using Nelder-Mead search alone for sparse and noisy simulated data. The noisy data were simulated by adding 20% proportional error to the true simulated observations.

Results: All parameters of the KP model are structurally locally identifiable. We estimated the tumor antigenicity *c* and growth parameters (*r2, b*) with all other parameters held fixed since we contend there is rationale for obtaining the other parameters from literature or via *in vitro* studies [2,4]. We found that the ELS method was unable to accurately estimate parameters, resulting in highly discordant predictions versus the observations. The ACS method yielded estimates very close to nominal and the predictions closely matched the simulated observations with low percent bias. The parameters *r2* and *c* had percent bias of 7.21% and 6.8% for sparse noiseless data and 1.05% and 1.4% for noisy data with 20% proportional error respectively. The growth parameter *b* had percent bias of 80% for noiseless data and 120% for sparse noisy data respectively. A sensitivity analysis for parameter *b* was performed and it was observed that the predicted concentrations are insensitive to fluctuations in parameter *b.* By comparison, the percent biases of parameter estimates was very large for the ELS method, in the order of 1000.

Conclusions: Our analysis supports the suggestion that deterministic chaotic systems are well estimated using a deterministic approach and demonstrates that the ACS method combined with Nelder-Mead search is a highly effective and robust method for estimating the parameters of an exemplary chaotic system of noisy and sparsely sampled Ordinary Differential Equations.

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IV-61: *Eduard Schmulenson* A physiologically-based pharmacokinetic modeling approach to assess the impact of chronic kidney disease

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Objectives: Chronic kidney disease (CKD) is a general term for various irreversible disorders of kidney structure or kidney function. It has an impact on the pharmacokinetics of numerous drugs and consequently, concepts of dose adjustments according to the renal function of CKD patients have been established. The progression of CKD affects nearly all organs and body systems, revealing the need to characterize its systemic nature by applying a quantitative systems pharmacologic approach. The aim of the study was to develop a physiologically-based pharmacokinetic (PBPK) modeling approach to understand and predict drug exposure in patients suffering from CKD of different stages.

Methods: A systematic literature search was conducted to identify and to inform pathological conditions of CKD patients which possibly have an impact on the pharmacokinetics of drugs. Within the Open Systems Pharmacology Suite [1] the parametrization of the physiological changes was performed according to the CKD classification [2] by calculating fractional changes along the staging system. An incorporated aging database [3] was used to distinguish between age- and disease-related alterations. The uncertainty of each parameter was described by calculating a Taylor series expansion.

In order to qualify the parametrization, PBPK models of four paradigm compounds (gentamicin, amikacin, gadodiamide, zanamivir) which are eliminated solely by glomerular filtration were built. The mean prediction error (ME) and the root mean squared prediction error (RMSE) were calculated to assess the predictive performance of the diseased-informed fractional changes compared to uninformed simulations in which solely the glomerular filtration rate was adjusted.

Results: The identified parameters included pathophysiological alterations of the kidney blood flow, kidney volume, hematocrit, gastric emptying time and concentrations of drug binding plasma proteins. The re-parametrization was applied to describe the exposure of the four paradigm compounds. The calculations of ME did not indicate a bias except for two simulations of gentamicin in CKD stage 5 or end-stage renal disease (ESRD) patients. Disease-informed simulations of patients with CKD stages 2, 3 and 4 were more precise than the uninformed ones (relative improvements of 15% to 22%) except for one simulation of patients with CKD stage 3 after administration of zanamivir. The precision of the prediction of ESRD patients receiving gadodiamide improved by 54%, whereas the simulations of gentamicin and amikacin in ESRD patients did not indicate an improved predictive performance comparing to the respective uninformed simulations.

Conclusions: An accurate and precise prediction of drug exposure for paradigm compounds eliminated by glomerular filtration for different stages of CKD was successfully conducted. The lack of improvement of predictive performance of simulations in ESRD patients suggests that the potential involvement of dialysis and the progression of uremia may require an extension of the model. However, this PBPK modeling approach provides support for specific considerations regarding clinical trial design and pharmacotherapy for patients suffering from CKD.

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IV-62: *Teun Post* An HCV nucleoside inhibitor MK-3682 minimal PBPK-PD model for application in hypothesis generation regarding metabolic pathways and perturbations under various conditions

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Objectives: MK-3682 is a uridine nucleoside monophosphate prodrug inhibitor of HCV NS5B RNA polymerase. To support the understanding of its metabolism and perturbations therein linked to efficacy, a minimal physiologically based pharmacokinetic-pharmacodynamic model was developed. This framework integrated the complex interplay between MK-3682 and its C- and U-nucleoside metabolites' (M5 and M6) plasma pharmacokinetics (PK). Following metabolism in the liver, the projected active phosphorylated form (nucleoside triphosphate; NTP), which does not circulate, was linked to efficacy. The in vitro and clinical data of various intrinsic and extrinsic factors, such as formulation (tablet, capsule, IV), DDI with CYP3A4/P-gp perpetrator itraconazole and subject status (healthy volunteers or HCV patients) were included.

Methods: A minimal PBPK model approach, based on Brill et al [1], was applied to characterize the PK of MK-3682 and its metabolism to M5 and M6 in both the gut wall and the liver. PK data from five phase I studies and one phase I/IIa study were used (n=217 subjects). Phase I studies included PK data after IV and oral (capsule or tablet) administration, and after administration of MK-3682 in the presence of the strong CYP3A4/P-gp inhibitor itraconazole. The phase I/IIa study included data from healthy volunteers and HCV patients, including an itraconazole DDI arm in HCV patients. Dose levels of orally administered MK-3682 ranged from 50-750 mg given as single and multiple doses. The minimal PBPK model was developed in a stepwise approach. First, the base structure of the model was established using IV and tablet data after MK-3682 monotherapy in healthy volunteers. Subsequently, the influence of formulation, HCV status and itraconazole coadministration on the PK of MK-3682, M5 and M6 were investigated. Finally, the individual *posthoc* parameters from the PK model were used as input for investigating the link between the projected NTP and viral load (VL). The model was developed using the non-linear mixed-effects modelling software NONMEM V7.2.0 [2] and data processing was done using R [3] and RStudio [4].

Results: The minimal PBPK model leveraged knowledge of known/hypothesized metabolic pathways and provided a good fit to the PK data of MK-3682, M5 and M6. The model captured differences in PK between formulations, between HCV patients and healthy volunteers and between MK-3682 monotherapy or coadministration with itraconazole. The model consisted of gut wall, portal vein and liver compartments for MK-3682, while empirical compartments were used to describe the metabolic pathways to M5 and M6. Separate formation pathways of M5 and M6 in the gut wall and in liver could be identified. This was particularly important for investigating the link between PK and efficacy, as only M5 and M6 formed in liver are derivatives of NTP. In order to capture the less than proportional PK observed for M6 after oral dosing, M6 uptake in gut depended on the estimated gut M6 concentration. This did not affect MK-3682 and M5 PK, which increased linearly with dose. Although presence of an M5 gut formation route was not initially anticipated, inclusion of this route was needed to describe the PK for M5 after oral dosing. A concentration-dependent rate between the two NTP compartments in liver (UXP and CXP) was needed to fit single as well as multiple dose data simultaneously. The larger effect on viral load in the presence of itraconazole could be explained by the model as well. Due to inhibition of gut metabolism and/or inhibition of active transport from the gut wall via P-gp, more MK-3682 reaches the liver. This results in higher NTP concentrations, which explains the higher log drop in viral load.

Conclusions: The minimal PBPK model, in combination with the identified link between projected NTP and viral load, provided a better understanding of the complex hypothesized metabolism of MK-3682 and of the relationship between plasma PK and projected liver NTP. The model captured differences in PK between formulations and between patients and healthy volunteers. In addition, the enhanced efficacy observed in patients with HCV when itraconazole was coadministered with MK-3682 was explained by the model. Overall, this framework supported and guided hypothesis generation and understanding regarding underlying metabolic pathways and perturbations under various conditions, including impact on downstream viral load.

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IV-63: *Manuel Prado-Velasco* New approach based on physiological modelling to compute the bioavailability using the PhysPK biosimulation system

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Introduction and objectives: According EMEA *bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form, and becomes available at the site of action* [1]. Due to the difficulty to perform that measurement, the rate and amount of the active substance delivered to the systemic circulation are accepted as surrogate indices.

The amount related bioavailability, *F*, is defined as the proportion of a drug which is absorbed and available to produce systemic effects. Although *F* could vary with time, standard mathematical equations neglect time dependency of *F*, and use an asymptotic or steady-state values for unique and multiple drug dose, respectively. Additional equations are needed in the case of non-linear clearance, both for single and multiple doses [2]. More complications emerge in the case of extensive first-pass effect in lungs [1].

The key point is that despite the importance of bioavailability in bioequivalence studies, current procedures are limited to stationary values and systemic circulation. This study presents a novel approach to calculate *F(t)* in the site of action by means of PBPK models.

Methods: The following stages define the procedure used to develop the approach

1. Current mathematical equations to calculate *F*, with emphasis in their assumptions, are firstly reviewed.
2. New mathematical formulations for *F(t)* are comprehensively presented. These equations have been implemented into signal computing elements of the PhysPK© biosimulation system's Widgets library.

Several scenarios were defined to compare the new equations against standard ones using a Tacrolimus PBPK model based on a previous published one [3]. The Tacrolimus model was validated against the data set of a pediatric clinical study carried out with 20 patients. A non-Compartmental Analysis (NCA) was finally executed to calculate standard *F* values, which were compared to the *F* values provided by the PBPK model

Results: The novel equations for *F* gave steady-state and asymptotic values equal to those ones of standard equations in systemic circulation, both for single and multiple dose scenarios, and for linear and non-linear clearance, through PBPK model simulations.

The *F* values obtained in the NCA with the data set values of the clinical study were in agreement with the simulation values of the adjusted Tacrolimus PBPK model, both for standard and new equations.

In addition, the simulation results of the adjusted Tacrolimus PBPK model included temporal values of *F(t)* in target anatomical regions, kidneys and liver.

Conclusions: It has been defined a new approach to measure the dynamic value of bioavailability, *F(t)*, based on population fitted PBPK models and new mathematical formulations of *F(t)*. The procedure was

implemented in the PhysPK© biosimulation software, which makes easy the addition of new computational metrics by means of an object-oriented, multilevel modelling, and graphic user interface system.

Data of Tacrolimus plasmatic concentrations from a 20 patient's clinical study were used to validate a Tacrolimus PBPK model successfully. This model, implemented in PhysPK, was the basis for the execution of a computational experiment that run simultaneously non-compartment calculations (NCA) and compartmental simulations, giving standard and novel bioavailability *F(t)* values, besides other standard plasmatic metrics (Cmax, AUC-12h, etc.).

Results shown that standard equations of *F* for steady – state and asymptotic plasmatic values computed from compartmental simulations accurately match to NCA values. The new equations for *F(t)* delivered the same accurate values of steady – state and asymptotic values, but they added their temporal evolution and the availability to measure it other anatomic regions like kidneys and liver.

Despite temporal values of *F* were not contrasted against experimental temporal values different of asymptotic and steady – state scenarios, the good agreement to the standard NCA values, together with the accurate predictions of a well-defined and validated PBPK model, suggest that this **physiology based model approach to calculate the bioavailability** could be considered an alternative technique to current standards in those cases where the dynamics of *F* could have a significant influence in therapeutic response.

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IV-64: *Jens Przybilla* Epigenetic modelling of DNA demethylation therapy in Acute Myeloid Leukemia

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Objectives:

In Acute Myeloid Leukemia (AML) the number of associated gene mutations is low but some of them are related to epigenetic modifiers. One frequently observed epigenetic pathology is DNA hypermethylation of gene promoters which often results in modifications in gene-expression and a blockade of differentiation. Treatment of AML patients with DNA methyltransferase (DNMT) inhibitors as Azacitidine and Decitabine results in global hypomethylation of genes and thereby, can lead to a reactivation of the natural differentiation capability of leukemia cells. However, due to the reversibility of epigenetic changes, hypermethylation and differentiation blockade often return after stopping the treatment.

We developed a single cell and multiscale computational model of epigenetic regulation of transcription in order to provide a mechanistic understanding of the DNA (de-) methylation process in AML and to construct a predictive model of DNA demethylation treatment strategies. Our general objective is to develop new hypothesis for epigenetic therapies by in silico simulations of our mechanistic model.

Methods:

Our computational model considers a cell population of individual cells. The cells do not interact. Each cell contains the same random genome that generates an artificial transcription factor network which is regulated by itself. Activating and repressing transcription factors are equal distributed. The main focus in our modeling is the additional layer of transcriptional regulation by epigenetic regulatory factors. These factors are DNA methylation of promoters, the activating histone modification H3K4me3 and the repressing histone modification H3K27me3. In our model, both histone modifications are directly incorporated in transcriptional regulation. In contrast, DNA methylation is regulated by binding of histone modification enzymes. By computational simulations, we analyze promoter hypermethylation scenarios referring to DNMT dysfunction, decreased H3K4me3 and increased H3K27me3 modification activity and accelerated cell proliferation. We quantify differences between these scenarios with respect to gene repression and activation. Moreover, we compare the scenarios regarding their response to DNMT inhibitor treatment alone and in combination with inhibitors of H3K27me3 histone methyltransferases and of H3K4me3 histone demethylases.

Results:

We found that the different hypermethylation scenarios respond specifically to therapy, suggesting that a failure of remission originate in patient specific deregulation [1]. We also observed that inappropriate demethylation therapy could also be detrimental in the sense that it could result in increased deregulation. As an example, our results suggest that application of high DNMT inhibitor concentrations can induce unwanted global gene activation if hypermethylation originates in increased H3K27me3 modification.

Conclusions:

Our modelling results underline the importance of a personalized therapy requiring knowledge about the patient-specific mechanism of epigenetic deregulation. From our model simulations we conclude that DNA demethylation therapy allows the reestablishing of a natural gene expression state of leukemia cells by the regeneration of the histone modification states.

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IV-65: *Alicja Puszkiel* Quantitative evaluation of the impact of CYP2D6 genetic polymorphisms on pharmacokinetics of tamoxifen and its metabolites in breast cancer patients

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Objectives: To develop a population pharmacokinetic (PopPK) model describing the disposition of tamoxifen (TAM) and three of its metabolites in breast cancer patients and to investigate the impact of genetic polymorphisms of CYP2D6 on plasma levels of active metabolites: 4-hydroxy-tamoxifen (4-OH-TAM) and endoxifen (ENDO).

Methods: PK data for TAM and three metabolites (N-desmethyl tamoxifen [NDT], 4-OH-TAM and ENDO) come from a prospective, multicenter, 3-year follow up study including 888 patients starting treatment with TAM at 20 mg once daily. This report focuses on preliminary results from 209 patients. Plasma samples were available for each patient every 6 months during a 3-year period, i.e. at inclusion (before treatment start) and 24-hours post-dose at 6, 12, 18, 24, 30 and 36 months. Plasma concentrations of TAM and metabolites were measured by a validated UPLC-MS/MS method [1]. Patients were genotyped at inclusion for single nucleotide polymorphisms (SNP) in the gene encoding for CYP2D6 and classified into poor (PM), intermediate (IM), extensive (EM) or ultrarapid metaboliser (UM) based on the presence of functional (*1), reduced function (*9, *10, *17, *41) or non-functional alleles (*4, *6, *7) and the number of CYP2D6 copies (*5 or gene duplication). Concentration-time data were analysed using non-linear mixed-effects modelling in NONMEM 7.4 using FOCE with interaction option. The impact of CYP2D6 activity on certain metabolic rate constants was tested according to the power equation and was considered significant if the objective function value (OFV) and the interindividual variability (IIV) of the estimate of corresponding parameter decreased significantly.

Results: PK data for TAM and the three metabolites (n = 934 samples) were analysed simultaneously with a four-compartment model with ENDO formed from either NDT or 4-OH-TAM, themselves formed from TAM. The absorption of TAM from gut compartment was described by a first-order rate constant ka. Volumes of distribution (Vd) of the metabolites were not identifiable and were fixed to a value of Vd of TAM previously reported in the literature [2]. The formation of metabolites was described by linear conversion as follows: k_{23} is the conversion rate constant of TAM to NDT, k_{24} TAM to 4-OH-TAM, k_{35} NDT to ENDO and k_{45} 4-OH-TAM to ENDO. Since TAM, NDT and 4-OH-TAM can follow other metabolising pathways which do not lead to the formation of the metabolites accounted for in the model, the inclusion of elimination rate constants for TAM (k_{20}), NDT (k_{30}) and 4-OH-TAM (k_{40}) were tested by comparing the OFV of models with and without each of these constants. Inclusion of k_{30} resulted in improved goodness-of-fit plots and a significant decrease in the OFV, therefore it was retained in the model. The elimination rate constant of ENDO (k_{50}) was fixed to a value previously reported in the literature [2]. The residual error was coded separately for each compound using a proportional model. Inclusion of CYP2D6 activity as covariate on k_{35} significantly decreased OFV (ΔOFV = -145). IIV in k_{35} decreased from 71.3% in the base model to 47.5% in the final model. The mean (relative standard error, RSE%) [CV% for IIV] estimates of the final model were: k_{23} = 6.94 x 10^{-3} h^{-1} (2%) [29.5%], k_{24} = 3.64 x 10^{-5} h^{-1} (34%) [73.6%], k_{35} = 4.48 x 10^{-4} h^{-1} (5%) [47.5%], k_{30} = 3.94 x 10^{-3} h^{-1} (3%) [44.6%] and k_{45} = 1.26 x 10^{-3} h^{-1} (33%). k_{35} decreased by 84.9% and 69.9% in PM and IM patients,

respectively, and increased by 58.0% in UM patients, compared to EM patients. Residual error estimates were 25.3% (7%), 26.3% (6%), 29.6% (8%) and 31.5% (7%) for TAM, NDT, 4-OH-TAM and ENDO, respectively. The correlation between TAM and NDT residual error was 79.1% (8%) and between 4-OH-TAM and ENDO 81.7% (10%). Eta-shrinkage was less than 7% and epsilon-shrinkage was less than 9%.

Conclusions: The developed model gave a good description of steady-state concentrations of TAM and three of its major metabolites. CYP2D6 activity significantly influenced the formation of ENDO from NDT. Future analyses will focus on inclusion of the three remaining metabolites in order to develop a joint PK model describing major metabolism pathways of TAM. The developed model could be useful to establish recommendations for monitoring of plasma concentrations of TAM active metabolites and to individually adjust the dose based on previously proposed target plasma ENDO concentration [3].

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IV-66: *Luis Quintairos Domenech* Pharmacodynamic modelling of biomarkers in kidney transplantation: a transformed binary data population approach

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Objectives:

Despite advances in immunosuppression, allograft rejection still remains a challenge in solid-organ transplantation. Micro RNA-155-5p (miRNA155) has been described as a positive regulator of inflammatory responses that participates in adaptive immunogenicity controlling T-CD4+ cells differentiation. Chemokine interferon inducible (CXCL10) is also a promising biomarker of short- and long-term kidney graft function. Previous results of our group and others, showed that urinary pellet levels of miRNA155 and urinary CXCL10 production could play a key role of prognosis and diagnosis in risk of acute rejection in kidney transplantation [1]. The objective of the present study was to develop a binary pharmacodynamic model in adult kidney transplant patients, establishing a relationship between miRNA155 and CXCL10 levels, tacrolimus and MPA exposure and the probability of acute rejection.

Methods:

Data from 58 kidney transplanted patients from the European multicenter study IMAGEN (EudraCT - number: 2013–001817-33) were analyzed in the present work. All[H1] patients received tacrolimus, mycophenolate mofetil (MPA) and methylprednisolone. Details about patients and therapies are specified elsewhere [1]. Samples were obtained at the 1^{st} week and 1^{st},2^{nd},3^{rd} and 6^{th} months post-transplantation. Trough tacrolimus and MPA concentrations, urinary pellet expression of miRNA155 and urinary production of CXCL10 were determined on each occasion. The final pooled data set included 193 observations of each biomarker, tacrolimus and MPA. Patient demographic characteristics, as well as occurrence of acute rejection or infection, and cytomegalovirus (CMV) or BK virus (BKV) presence were recorded.

A logistic regression model was used to investigate the relationship between either biomarker or/and drug exposure and the probability of acute rejection occurrence. The efficacy data (rejection event or not) were evaluated as binary data with 0 indicating no rejection and 1 indicating rejection occurrence. The probability of the observed score was linked to biomarkers and drug exposure through the logit transformation, to ensure that the probability falls between 0 and 1. The influence of all physiologically plausible covariates and the effect of time as a linear model, on graft function outcome, were tested. Between subject variability (BSV) was tested on all parameters. NONMEM 7.4 [2] software with FOCE method with Laplacian was applied throughout all building process.

Selection of the best model was performed according to: i) objective function value (MOFV), ii) plausibility of parameter estimates and precision (given a %relative standard error) iii) visual predictive check plots for categorical data after 1000 simulations. The acceptance criteria for a covariate into the model was a ΔMOFV of at least -3.84 ($p<0.05$) and a reduction or at least no increase in the unexplained variability in the model. R software 3.3 [3] and vpc R package [4] were used as graphical evaluation tools, and Pirana software [5] was also used as a support tool.

Results:

8 out of 58 patients developed an acute rejection event and 4 of them, developed a second acute rejection event during the study. 14, 9 and 34 out of 58 patients developed CMV, BKV and nonspecific infections, respectively, at certain occasions, but no infection episodes were observed at the same time of the any of the acute rejection events.

No statistically significant relationship was found between exposure of tacrolimus or MPA and the clinical outcome. The linear effect of time did not improve the fit. BSV was only included on the baseline (B0) (10.8% (36%RSE)). The Inclusion of miRNA155 significantly improved the baseline model (ΔMOFV[clinic1] -17.658) and the posterior inclusion of CXCL10 (ΔMOFV[clinic2] -7.857) led to a reduction 51.71% in BSV. None of the other tested covariates (infection, CMV and BKV) were identified as significant predictors. The final logit function was as follows:

Log (OR)=B0 + B1*miRNA155 + B2*CXCL10

Being, B0 (-8.3(17%RSE)) the baseline effect and B1(5.7(18%RSE)) and B2(0.0071(30%RSE)) the slopes of the miRNA155 and CXCL10 effects, respectively.

Conclusions:

Both miRNA155 and CXCL10 were identified as predictors of the risk of developing an acute rejection in early kidney post-transplant patients while no influence was found for neither tacrolimus nor MPA, confirming previous results [1]. Further studies with a larger sample size would be required in order to confirm the current findings.

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IV-67: *Hanne Refsgaard* Steps Towards a Robust Generic Method for Deconvolution Directly on Pharmacokinetic Profiles

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Objectives: The objective of the present investigations is to develop a robust generic method for deconvolution directly on pharmacokinetic (PK) profiles. Classic deconvolution methods use information from compartmental modelling and often the variability in the intravenous data is neglected. We have evaluated and further developed a maximal entropy method [1, 2] to perform deconvolution directly on intravenous and extravascular profiles without assuming the underlying compartmental model.

Methods: We constructed simulated datasets which mimicked preclinical PK datasets both in terms of noise, sampling frequency and parameters of underlying compartmental models. The simulated datasets were two intravenous datasets produced by stochastic simulations with either an underlying one- or two-compartmental model. Two extra vascular datasets where likewise produced with underlying one- or two-compartmental models and by using a known input rate. The maximal entropy method [1, 2] tries to balance fitting of the extravascular profile with flattening of the estimated absorption rate profiles. Previous work has assumed that the unit impulse responds function, e. i. information from the intravenous data, is known and without noise. We modified the maximal entropy method by using scaled intravenous profiles directly as unit impulse responds functions and tested the method on the simulated data. Furthermore, classic deconvolution methods based on compartmental modelling on the simulated intravenous datasets were used on the simulated extravascular dataset for comparison.

Results: Absorption rate profiles were determined by deconvolution directly on the simulated PK profiles applying a modified maximal entropy method developed in the present work. The obtained absorption rate profiles were similar to the theoretical absorption rate profile for a simulated one-compartmental dataset, however for the first time point the determined absorption rate was determined higher than the theoretical. This was also seen with the two-compartmental dataset.

Conclusions: A generic method for deconvolution directly on PK profiles was developed and tested on simulated datasets. The method resulted in similar absorption rate profiles as expected from the theoretical absorption rate, except for the initial time point(s).

The next steps in the development of the generic deconvolution method will include investigations of effect of variability in both the intravenous and extravascular data for deconvolution results especially.

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IV-68: *Theo Reijmers* Population PK Modelling of Treosulfan in Paediatric Allogeneic Transplant Patients

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Objectives: Treosulfan, a bifunctional alkylating prodrug, is currently being developed by medac GmbH as a component of conditioning treatment prior to haematopoietic stem cell transplantation (HSCT) in adults and children. An initial population PK model was developed to select dosages for new trials in paediatric patients from 1 month to 18 years of age. During interim analyses this model was updated with new paediatric PK-data to contribute (in addition to clinical safety and efficacy data) to decision finding for potential modification of dose recommendations for the ongoing medac-sponsored trials MC-FludT.16/NM (EudraCT-Number: 2013-005508-33) and MC-FludT.17/M (EudraCT-Number: 2013-005508-33). In addition to the data covering different age groups the model also needed to handle data that was measured with different bioanalytical methods.

Methods: The initial population PK model for treosulfan was developed with NONMEM using treosulfan PK-data from 7 previously conducted clinical trials consisting of 93 adults and 23 children (age range: 0.4 to 17 years) [1]. To recommend doses in paediatric patients, the potential influence of certain covariates was investigated. Next, this model was updated on a regular basis using PK-data from the new paediatric allogeneic HSCT trials MC-FludT.16/NM (17 children; recruitment ongoing) and MC-FludT.17/M (59 children; recruitment closed). For modelling different subpopulations (adults vs. children) both a dichotomization approach and use of a Bayesian prior were evaluated [2].

Results: The initial population PK model for treosulfan consisted of 2 compartments with first order distribution and elimination processes. Covariate analysis revealed that BSA was the only relevant covariate for clearance (allometric coefficient CL-BSA = 1.29) and volumes of distribution (allometric coefficients V1-BSA = 2.05 & V2-BSA = 1.24). The model provided an adequate fit to the data and model diagnostics revealed no relevant bias. The dose recommendation for treosulfan was 10 g/m^2 (BSA<=0.5m^2), 12 g/m^2 (BSA between 0.5 m^2 and 1.0 m^2), and 14 g/m^2 (BSA>1.0 m^2). The functional relationship between clearance and BSA within the estimated population PK model was applied to derive dose recommendations for the new paediatric trials. The update of the initial PK model contained a shift parameter (on model prediction parameter F in $ERROR) that allowed modelling of data from the new paediatric trials measured with a different validated bioanalytical method. Also, an additional covariate-model parameter relationship between BSA and intercompartmental clearance was identified. Both the dichotomization and Bayesian approach gave similar results. Ultimately the approach closest to the initial model, the dichotomization approach, was chosen. All model parameters could be estimated with adequate precision (RSE < 25% & 45% for fixed and random effect parameters). Bootstrap results were in good agreement with results directly obtained from NONMEM. VPCs of the updated model showed a certain bias for the largest BSA paediatrics group (BSA > 1 m^2). Concentrations between 2 and 3 hr after start of infusion are within the prediction range but almost all concentrations are above the median of the simulations for this group. According to the model-based updated dosing scheme, for children with a BSA of 0.4, 0.5, 0.9 and 1.0 m^2 a limited increase in dose is considered based on these interim data.

Conclusions: The population PK model for treosulfan is robust and does accurately predict exposure in children. Inclusion of interim PK-data from newly included paediatric patients resulted in a significant update of the model. From a population PK modelling perspective, a slight refined dosing for some patients was recommended.

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IV-69: *François Riglet* Multiple response modelling of mycophenolic acid pharmacokinetics in adult patients with transplanted kidneys by population approach

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Objectives:
Mycophenolic acid (MPA) is an immunosuppressant drug used to prevent graft rejection, which acts as an inhibitor of inosine-monophosphate dehydrogenase (IMPDH). It shows a narrow therapeutic index, especially in renal transplant recipients because of its great between-patient variability [1,2]. So currently, in France, Therapeutic Drug Monitoring (TDM) of MPA is carried out by evaluating the Area Under the Curve (AUC_{0-12}) of total MPA in plasma in order to improve long-term allograft survival with adequate dosing [3]. However, because MPA mechanism of action occurs into peripheral blood mononuclear cells (PBMCs), it is reasonable to think that carrying out TDM at cellular level could be more efficient to predict drug efficacy or adverse effect. The aim of the present study was to build a pharmacokinetics (PK) model using a population approach to describe MPA total and unbound concentrations in plasma and into PBMCs in adult kidney transplant recipients. We hoped to quantify average PK parameter values and their respective between and within subject variability (B and WSV), in this specific population, and to understand the origins of MPA PK high variability.

Methods:
PK data for MPA were available from 78 patients, included in the CIMTRe study, on 4 occasions; 15 days (D15), 1 month (M1), 2 months (M2) and 6 months (M6) after renal transplantation which amounted to 1993 PK samples. All patients originally received a dose of 1000 mg twice daily of mycophenolate mofetil (MMF), ester prodrug of MPA. Plasma total and unbound MPA as well as MPA in PBMCs concentration-time profiles were collected over 12h after the drug intake. Population analysis was performed using non-linear mixed-effects modelling with the Monolix® software.

Results:
A three-compartment PK model with a zero order absorption ($Tk0_u$=1.85 h, BSV=83%) and a first order elimination (Cl_u/F= 965 $L.h^{-1}$, 41%) was used to describe all unbound MPA concentration–time data at month 1 after renal transplantation. Unbound MPA distribution was described with one central compartment (Vc_u/F=1430 L, 13%), one peripheral compartment (Vp_u/F=37800 L, 127%) and an intercompartmental clearance (Q_u/F=2330 $L.h^{-1}$, 50%). The third compartment described the distribution of the drug in the PBMCs with three estimated parameters: the input rate into the cell ($Clin_u/F$ = 28.5 $L.h^{-1}$, 80 %), the output rate from the cell ($Clout_u/F$ = 0.76 $L.h^{-1}$, 69%) and the volume of distribution in the cells ($Vcell_u/F$ = 223 L). A proportionality factor parameter described the linear link between plasma unbound and total MPA concentrations (Bmax = 52.8, 20%). With this model, the unbound MPA fraction obtained was then 1.86%, which is in agreement with the data of MPA literature. From this model, we derived MPA exposures in the plasma (total and unbound) and in the cells. We estimated a $MPA_{unbound}$ AUC_{0-12} median = 0.93 [0.79 - 1.22] $mg.h.L^{-1}$ and a MPA_{total} AUC_{0-12} median = 49.35 [41.98 - 65.02] $mg.h.L^{-1}$. Such exposures correspond to a clearance of MPA_{total} Cl_t/F = 20 $L.h^{-1}$. All these parameters were close to values found in the literature [2]. Lastly, the $MPA_{cellular}$ AUC_{0-12} median was estimated at 29.16 [13.94 – 53.62] $mg.h.L^{-1}$.

Conclusions:
The population PK model developed during this study successfully characterized MPA pharmacokinetics in adult patients with transplanted kidneys, including unbound and cellular pharmacokinetics. Although modelling of D15, M2, and M6 samples and covariates analyses are still under study, this first model can help predict how much MPA molecules can actually inhibit IMDPH in the cells.

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IV-70: *Christer Rimmler* Evaluating New Dosing Strategies for the Use of Cefuroxime in Perioperative Antibiotic Prophylaxis using PBPK

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Objectives:

Optimization of the perioperative antibiotic prophylaxis (PAP) is still a matter of debate. Despite existing guidelines and recommendations, there are important issues of uncertainty regarding the timing and dose before incision and the intraoperative follow-up administrations. Another issue is the tissue penetration of the antibiotics used for PAP. Therefore, we collected perioperative plasma and tissue samples from 25 patients receiving cefuroxime. To evaluate effects on the PK triggered by the alteration of physiological conditions during surgery, we included relevant changes in the final model.

Methods:

We collected plasma and lung tissue samples from 25 thoracical surgery patients (18 to 77 years). After induction of anesthesia, a dose of 1.5 g cefuroxime was administered intravenously. Another 1.5 g cefuroxime was given every 2.5 h thereafter. On the basis of our previous model [1] we used PK-Sim®/MoBi® [2] for population simulations and a scale-up from the fitted tissue concentrations to interstitial concentrations. We simulated alternative dosing regimens in varying populations (see below) and tested the difference between long-term infusions and standard short infusions. The simulated populations, which were in line with our study population, show different BMI levels, kidney functions, age and gender. For beta-lactams the relevant PD-target to achieve a maximal bactericidal and bacteriostatic effect, is the free drug concentration exceeding the pathogens minimal inhibitory concentration (MIC) for 60-70% and 35-40% of the time during the dosing interval in the targeted tissue. To reach this target, it is advocated that the blood concentrations should also exceed the MIC by a factor of 4 to 6 [3]. As targeted tissue we used the free unbound plasma and the lung interstitial unbound concentrations. Test pathogens for the definition of the MIC are *Staphylococcus aureus* and *Escherichia coli* which are most relevant for surgical side infections. The MIC values were taken from EUCAST Clinical Breakpoint Tables [4] and modified as described above.

Results:

The adjustment of the model according to the physiological changes during surgery improved the performance for the individual simulations (MPE = 1.4% and MAPE = 29.0%), with 84.5% of predicted plasma concentration being within 50% range of the observed values. The lung tissue concentrations could also be described adequately (MPE = 7.0%; MAPE = 34.3%). After subdividing the population into three groups accordning to their glomerular filtration rate (GFR) ranging from 40-80, 80-120 and 120-160 mL/min, the population simulations present adequate predictions as well (MPE = 10.4%; MAPE = 27.3%). In the low GFR population, the given dosing regimen leads to a protection for about 1.9 hours. However, in the middle and the high GFR group, the protection persist only 1.0 and 0.8 hours, respectively. In

simulations, bolus of 1.5 g cefuroxime and long-term infusion of 3 g for 3 hours, leads to a protection for 4.6, 5.4 and 7.5 hours respectively, without giving more antibiotics as in the old dosing schedule in sum.

Conclusions:

We were able to give clear dose recommendations in the field of perioperative antibiotic prophylaxis. Our results show that the kinetics of cefuroxime is influenced by age and kidney status, not by gender, BMI or the surgery [1]). The use of cefuroxime for perioperative prophylaxis to prevent staphylococcal surgical site infections appears to be reasonable and recommendable. According to our results, the use of cefuroxime for perioperative prophylaxis against *Escherichia coli* in abdominal surgeries, using the described dosing regimes appears to be at least questionable. With our dose recommendations we provide a solution for this issue.

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IV-71: *Christelle Rodrigues* A population pharmacokinetic model taking into account protein binding for the sustained-release granule formulation of valproic acid in children with epilepsy

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Objectives: Valproic acid (VPA) is an antiepileptic drug widely used in the pediatric population. A sustained-release (SR) granule formulation facilitating oral drug intake by children is available at a recommended mean daily dose between 20 and 30 mg/kg [1]. No pediatric PK data are available to date for this SR granule formulation. So, the present work primarily aimed to develop a population PK model for this form in children with epilepsy. Afterwards, the final model was used to evaluate if dosage recommendations are adequate to obtain a trough concentration (Ctrough) within the reference range of 50-100 mg/L [2] and, if not, which doses would be more suitable. A secondary objective was to take into account the non-linearity due to the saturable protein binding in order to investigate the relationships between the doses and the total and free concentrations of VPA.

Methods: Ninety-eight children (1 – 17.6 years, 325 plasma samples) were included in the study. The model was built with NONMEM 7.3. One and two compartment models with zero or first order absorption and elimination were tested. Flip-flop was handled by adding a constant C to the model and by parameterizing ka to be equal to the sum of ke and C [3]. Three models were tested to describe the protein binding properties of VPA: 1) the addition of total daily dose (TDD) as a covariate on VPA clearance ; 2) a maximum effect (Emax) model where the TDD is also used as a covariate on CL [4]; and 3) a physiological protein-binding model [5] where unbound clearance and volume are estimated, and in which the total concentration is predicted from the apparent maximum concentration of the binding site for VPA (Bmax) and the apparent dissociation constant of VPA from plasma proteins (Kd). Since no unbound data was available in the present study, Bmax and Kd were fixed to their previously determined values of 130 and 7.8 mg/L, respectively [6]. Body weight (BW), age, sex, height, body surface area, creatinine, SGOT, SGPT and concomitant antiepileptic drugs were tested as potential covariates. Covariates were included in the model using a power function. Using the final model, Monte Carlo simulations were performed for doses of 20, 30, 40 and 60 mg/kg/day and BW between 10 and 70 kg, in order to predict steady-state Ctrough, maximum concentration (Cmax) and area under the curve (AUC) for the total and free drug. The probability to obtain total Ctrough between 50 and 100 mg/L was calculated and the associated free VPA range was determined.

Results: A one compartment model, with first-order absorption and flip-flop parameterization and linear elimination was used to describe the data. The saturable protein binding of VPA was best described with model 3). It allowed lower values of OFV and BIC in addition to be more physiological and mechanistic. Typical values for unbound VPA clearance and distribution volume were 6.24 L/h/70kg and 130 L/70kg respectively, corresponding to total values of 0.624 L/h/70kg and 1.3 L/70kg. Both parameters were related to body weight via allometric models. VPA total and unbound Ctrough, Cmax and AUC increased with the total daily dose and with BW. The range of unbound Ctrough corresponding to the total Ctrough within the therapeutic range was 4.2 – 14.8 mg/L. The highest probability to obtain a Ctrough within the target range for 10 kg children was obtained with a 40 mg/kg daily, whereas daily doses of 30 mg/kg and 20 mg/kg were

found appropriate for 20 – 30 kg and ≥ 40 kg children respectively. However, for these same doses, the exposure to unbound VPA could differ by 40 %.

Conclusions: The first pharmacokinetic model for a pediatric VPA formulation, sustained release granules, was developed, evidencing the occurrence of flip-flop due to its modified rate of absorption. This model took into account the nonlinear relationship between dose and clearance secondary to the saturable protein binding. The model also shows that VPA pharmacokinetic parameters are related to BW by allometric functions. If the present study supports the current dose recommendations of 20-30mg/kg/day, except for children under 20 kg who may need higher doses, it also highlights the need for further research on the pharmacokinetics/pharmacodynamic profile of unbound VPA.

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IV-72: *Leire Ruiz Cerdá* External validation of Systems Pharmacology Models of the Coagulation Network with published data

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Objectives: Several System Pharmacology (SP) models for the Coagulation Network are currently available in the literature (1-5). This type of models allows simulating the time profiles of the different components of the coagulation cascade and therefore, emulating the endpoints of several coagulation tests: (i) Thrombin Generation Assay (TGA), which captures Thrombin (FIIa) profiles, (ii) Prothrombin Time (PT) and (iii) activated Partial Thromboplastin Time (aPTT), which provide insight of the time needed to form the fibrin (FIIa) clot by the extrinsic or intrinsic pathway, respectively. In this regard, an unavoidable step is the evaluation of these SP models and their capacity to mimic the patho-physiological behavior by comparison with experimental data (6). Altogether, the objective of this work once the most relevant models were selected and implemented is to perform a validation exercise beyond the original experimental scenarios.

Methods: Two models were selected from the literature characterizing the entire coagulation network based on the inclusion of relevant components and reactions: Wajima, *et al.* (3) and Nayak, *et al.* (4). Firstly, these models were implemented using MATLAB's (v. 2017a) SimBiology 5.6 toolbox, including model components, reaction rates and equations. Importantly, a special effort was made in order to define units and make the models comparable. After the implementation, the figures shown in each study were reproduced to check and validate the implementation. Secondly, experimental data from normal individuals and trauma patients were collected from Menezes, *et al.* (6). These data included: (i) percentage of activation of blood protein factors II, V, VII, VIII, IX, X, and ATIII in each normal and trauma sample, (ii) TGA, (iii) PT and (iv) aPTT. For all the patients TGA, PT and aPTT were simulated using as initial condition the blood factors percentage reported. PT and aPTT were calculated as the time at which the 30% of the fibrinogen (Fg) was transformed to FIIa (7). Initial individual conditions for factors and proteins that were not reported were assumed equal to those listed in each of the selected models. Time course of FIIa and PT and aPTT were simulated and compared.

Results: The two models selected from the literature were satisfactorily implemented, as shown by the exact reproduction of the results presented in both manuscripts. In addition simulations of PT and aPTT metrics obtained using levels of several factors provided in Menezes *et al.* (6) for healthy individuals agreed well with the experimental observations. When a similar exercise was performed for the case of patients suffering from trauma, the above mentioned descriptors showed a relative error over 30%. When the time course of different coagulation cascade factors were simulated, discrepancies were found between the profiles obtained from the different models. Once a sensitivity analysis was performed, it was clearly seen that longitudinal profiles were very sensitive to initial conditions driven the experimental conditions, which might explain the discrepancies encountered. Interestingly, the sensitivity of the area under the FIIa concentration-time curve (AUC) to the initial stages of the coagulation process is very low and the discrepancies seen in FIIa concentration profile were not reflected in the corresponding AUC, which is the measure driving PT and aPTT.

Conclusion: Both selected models described very well data gathered from healthy individuals. However, this was not the case at least for patients suffering from trauma. Differences either in other non-measured elements from the coagulation cascade, or in model parameters between healthy subjects and patients are likely to be the reasons responsible for poor model performance, highlighting the need to focus on disease related process alterations when developing systems pharmacology. For outcomes obtained from ex-vivo sample manipulation a very detailed description of the experimental setting is required to ensure model reproducibility.

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IV-73: *Yevgen Ryeznik* Treatment allocation adaptive randomization methods in clinical trials with few individuals may influence model parameter estimation

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Objectives:

In dose-response studies with censored time-to-event outcomes, D-optimal designs depend on the true model parameters and the amount of censoring in the model. In practice, such designs can be implemented adaptively, by performing dose assignments according to updated knowledge of the dose-response curve at interim analyses [1]. It is also essential that treatment allocation involves randomization—to mitigate various experimental biases and enable valid statistical inference at the end of the trial [2]. In addition, since D-optimal designs target a decrease in uncertainty of estimated model parameters based on an optimal allocation of patients, then a randomization procedure which accurately achieves these targets (optimal proportions) is required. The choice of the randomization method becomes crucial when the sample size of a study is small, since some randomization procedures may have large shifts from the desired allocations. In this work, we perform a comparison of several adaptive randomization procedures that can be used for implementing D-optimal designs for dose-response studies with time-to-event outcomes with small to moderate sample sizes. In addition to standard comparisons of balance and randomness, we compare the procedures in terms of the quality of model parameter estimation. In addition, the effect of patient selection bias on parameter estimation is investigated. The results of this work should help clinical investigators to select an appropriate randomization procedure for their dose-response study.

Methods:

We consider a quadratic dose-response model for log-transformed Weibull event times that are subject to right censoring. For implementing the D-optimal designs, randomization procedures with possibly unequal target allocation are used. There exist many different randomization procedures which may target (un)equal allocation and keep a good balance across treatment arms. We compare several randomization procedures in terms of balance and randomness as well as estimation efficiency and impact on bias and uncertainty of parameter estimates. We consider single-stage, two-stage, and multi-stage adaptive designs. In order to investigate the effect of patient selection bias on model parameter estimation, we use the approach described in [3], but modified for a three-arm randomization setting.

Results:

A simple (and commonly implemented) completely randomized design is most variable and it is likely to deviate from the targeted D-optimal design for small sample sizes. This results in larger uncertainty in dose-response estimation and loss of design efficiency, especially for small sample sizes. Other randomization schemes achieve a tighter allocation balance, leading to higher efficiency, on average, and more accurate estimation of the dose-response relationship. For a multi-stage design with early stopping rules, there are randomization procedures that may require smaller sample size compared to completely random

allocation. The presence of selection bias has a negative impact on quality of estimation. The commonly used uniform (non-optimal) design has the worst performance in this scenario.

Conclusions:

The choice of a randomization procedure to implement optimal designs is important for model parameter estimation (quality of dose-response estimation), especially for small sample sizes. To our knowledge, this is the first investigation of the impact of randomization on model parameter estimation. For best performance, an adaptive multi-stage design with small cohort sizes should be implemented with a randomization procedure that ensures a “well-balanced” allocation according to the targeted optimal design at each stage.

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IV-74: *Oliver Sander* Detecting and Analyzing 5x Sit-to-Stand Tests from Accelerometer Data

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Objective

This work aims to study the relationship between the data collected by wrist-worn activity sensors during an unsupervised scheduled activity, the 5x sit-to-stand test (5xSTS), and electronic patient reported pain and stiffness outcomes (ePROs). It further investigates the feasibility and analyzability of the 5xSTS test.

Data

- 45 subjects participated in the study. Of those, 30 were arthritis patients (18 with rheumatoid arthritis, 10 with osteoarthritis, 2 with psoriatic arthritis), and 15 healthy volunteers
- Subjects were provided with a smartphone application to capture daily measures of pain/stiffness (ePRO) and with a wrist-worn activity sensor for a period of 4 weeks (Actigraph Link)
- Participating subjects were followed for 4 weeks. Unsupervised sit-to-stand tests were performed Mondays/Wednesdays/Fridays after getting up.

Methods

Data processing and 5xSTS detection

Raw accelerometer Actigraph data (sampled at 30 Hz) were post-processed in an automated pipeline including several correction steps (battery depletion), calibration (standardize acceleration during rest state), and transformation (Cartesian to spherical).

5xSTS time windows were extracted from the post-processed acceleration data in several selection stages. Selection was done by time of day (5xSTS performed in the morning), angle of arm crossed in front of chest, alternating elevation patterns, and specific acceleration patterns. The search for acceleration patterns is performed using regular expressions of consecutive strings of low/medium/high accelerations of varying lengths.

Correlation of 5xSTS duration and ePROs

Correlations between 5xSTS and daily ePRO responses on pain and stiffness were evaluated by linear mixed effects regression with the ePRO responses as dependent variables. Varying intercept as well as varying intercept & slope models were tested. The mixed effects regression approach allows accounting for correlations between observations from the same subjects, as well as assessing the contribution of additional covariates.

Validation

The overall data set was split into development, test, and validation set. Tuning of the detection procedure as well as the linear mixed effects modeling were performed on the development set and then checked against the other independent sets.

Results – Compliance

Compliance is bimodal (average 53%). No differences in compliance were found between healthy volunteers and patients. Most subjects with low compliance were highly compliant until they quit. Subjects performed the 5xSTS in a consistent and per-protocol manner in both supervised and unsupervised settings.

Results – 5xSTS « ePRO

Linear mixed-effects models are able to take into account individual patients' differences in pain threshold and fitness. Prediction discrepancy diagnostics do not show evident bias. The 5xSTS duration correlates with subjects' self-reported pain/stiffness, particularly with the responses given in the morning. Estimated coefficients are robust throughout the analysis.

Conclusions

- Unsupervised scheduled activities like the 5xSTS test are feasible in studies with acceptable compliance even with no strong reminders or real-time checks
- A semi-automatic workflow facilitates detection, data extraction and analysis from raw sensor data
- Device calibration: Even medical grade sensors need to be re-calibrated (consumer-grade sensor data may not allow re-calibration)

IV-75: *Stein Schalkwijk* Exploring Standard and Alternative Darunavir/Ritonavir Dosing Regimens for HIV-positive pregnant women using semi-mechanistic pharmacokinetic modeling

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Objectives:

Darunavir is administered as 800 mg once (QD) or 600 mg twice (BID) daily in combination with low-dose (100 mg) ritonavir (pharmacokinetic booster) as part of combination antiretroviral therapy for the treatment of HIV-positive pregnant women (darunavir/r). Therapeutic darunavir exposure in HIV-positive pregnant women is essential to prevent virological breakthrough, development of resistance and HIV transmission from mother to child. However, decreased total darunavir exposure (17%-50%) has been reported during pregnancy and limited data on unbound darunavir exposure are available. It is remains unclear whether standard darunavir/r dosing regimens provide adequate exposure throughout pregnancy. To support and inform the optimal choice of darunavir/r dosing in pregnancy we performed a semi-mechanistic population pharmacokinetic analysis.

Methods:

A simultaneous semi-mechanistic population pharmacokinetic analysis was conducted based on darunavir and ritonavir pharmacokinetic data (intensive sampling) in pregnant and nonpregnant (i.e. postpartum) women. Nonlinear darunavir protein binding was analyzed using a subset of total and unbound darunavir data and integrated in the final model. The final model was used to simulate total and unbound darunavir $AUC_{0\text{-}\tau}$, and C_{trough} during third trimester of pregnancy, as well as to assess the probability of therapeutic exposure based on reported total and unbound therapeutic targets. In total, 2601 plasma samples were available from 85 women, of which 1643 samples were taken during pregnancy. Corresponding unbound darunavir concentrations were determined in 74 plasma samples from 20 women, during pregnancy and postpartum.

Results:

The final model was developed in three steps. First, the darunavir protein binding dissociation constant and the maximal protein binding capacity were estimated based on nonlinear mixed-effects analysis of paired total and unbound darunavir concentrations in pregnant and nonpregnant women. Then, separate population pharmacokinetic models were developed for ritonavir and darunavir. Thereafter, an integrated pharmacokinetic model was developed, including the darunavir-ritonavir interaction and nonlinear darunavir protein binding. Pregnancy was found to reduce ritonavir relative bioavailability, decrease darunavir protein binding, and increase darunavir intrinsic clearance. As expected, decreased ritonavir exposure in pregnant women resulted in reduced inhibition of intrinsic darunavir clearance. The maximum inhibition (RSE) was 57% (28%) and the half maximal inhibitory ritonavir concentration was 0.09 mg/L (16%). Simulations demonstrated that in the third trimester of pregnancy, total darunavir exposure ($AUC_{0\text{-}\tau}$)

were 73% and 76% when compared to postpartum for darunavir/r 800/100 mg QD and 600/100 mg BID, respectively. Unbound darunavir $AUC_{0-\tau}$ were 90% and 93% compared to postpartum for darunavir/r 800/100 mg QD and 600/100 mg BID, respectively. Unbound darunavir C_{trough} were 79% and 88% compared to postpartum for darunavir/r 800/100 mg QD and 600/100 mg BID, respectively. The probability of therapeutic exposure during pregnancy was higher for standard BID dosing (100%) than for QD dosing (95.7%).

Conclusions:

The standard darunavir/r 600/100 mg BID regimen resulted in maximal rates of therapeutic exposure in pregnancy and was superior to 800/100 mg QD in terms of darunavir therapeutic exposure. Darunavir/r 600/100 mg BID should be the preferred regimen during pregnancy unless (adherence) issues dictate QD dosing. The value of alternative dosing regimens for pregnant women seems limited.

IV-76: *Stephan Schaller* Towards Predictions of Clinical Trial Outcomes: Combining PBPK and QSP within a Translational Diabetes Disease Platform

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Objectives: Clinical trial simulations are usually conducted at later stages of drug development typically requiring clinical data from Phase I/II/IIb. Our objective is to establish a digital platform for early prediction of clinical (trial) outcomes by leveraging physiological and mechanistic knowledge to translate early in-vitro and preclinical outcomes to the clinic.

Methods: An existing physiologically based pharmacokinetics/pharmacodynamics (PBPK/PD) quantitative systems pharmacology (QSP) model of the glucose-insulin metabolism for healthy individuals and type 1 diabetes patients [1–3] was translated to animal species most commonly used in preclinical diabetes research (rat, minipig and cynomolgus monkey) to create a physiologically- and mechanism-based translational modeling & simulation platform for diabetes. Animal physiology such as organ volumes, organ composition, blood and lymph flows was informed by the PBPK database of PK-Sim® as part of the Open Systems Pharmacology Suite (OSPS), version 7.2 [4]. Animal whole-body energy- and organ-specific glucose uptake and metabolism as well as properties of mechanisms underlying pharmacokinetics and pharmacodynamics of insulin and glucagon were informed by extensive literature search (non-exhaustive: [5–8]). This included basal concentrations for glucose, insulin and glucagon and secretion and turnover rates of insulin and glucagon. Missing experimental values for glucose metabolization in some organs and species was calculated using allometric principles based on information from other species.

Results: For model verification and to inform remaining uncertainties, the model was fitted to standard test experiments used in diabetes (oral- and intravenous glucose and intravenous insulin tolerance tests [9–14]). The animal models achieved high accuracy in describing the dynamics of animal systems pharmacology for glucose, insulin, and glucagon PK and PD on both, the quantitative and the qualitative level. The available datasets (mean) used for fitting were not representative regarding basal insulin levels when compared to available basal concentration data from large datasets. The animal models were thus fitted to the most prevalent of the reported basal concentration levels.

Conclusions: Structural and mechanism-based characterization of both the animal and human glucose metabolism is of great value when new treatments need to be analyzed and translated during transition from research to development. The captured structural and mechanistic knowledge allows for an informed extrapolation and thus accurate prediction of the treatment PK, the mode of action concept and the effect on whole-body glucose metabolism (e.g. effects on fasting plasma glucose, post-prandial glucose or HbA1c) when translating PK and PD from animals to humans. Leveraging its PBPK and QSP framework and a population of characterized in-silico diabetes patients, the platform allows population-level in-silico first-in-man and proof-of-concept evaluations for conceptualized treatments of diabetes. This can be done by translation of either pre-clinical outcome data or in-vitro compound properties at the drug discovery or lead-optimization stage. Another aspect that has proven invaluable is that even hypothetical compound properties can be translated into an estimate for efficacy in humans for an in-silico evaluation of ideas for novel treatment modalities prior to initializing costly in-vitro experiments and preclinical studies.

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S-01: *Kayla Andrews* Data Repository to Enable Organization and Collaboration for Pharmacometric Analysis

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Objectives: Successful implementation of model-informed drug development requires the interdisciplinary teams to collaborate efficiently and effectively. The management and organization of files used and produced during pharmacometric analyses throughout the drug development process can be a laborious task without a well-defined, logical directory structure. For successful collaboration, the ability to share data and documents with collaborators while enforcing granular application and file/data permissions is a requirement. The Data Repository, part of the KIWI Platform [1], is structured around interdisciplinary teams through the team management module which is encouraged to cross disciplines, and organizations. The Data Repository was specifically developed for pharmacometric collaboration in drug development to:

- Allow teams of users to upload, download, comment, review, version control and manage files and view metadata on those files relating to pharmacometric analysis.
- Provide folder structures to guide effective organization and collaboration on files and data
- Allow designated administrative users the ability to create teams and manage user access to groups of files depending on involvement.
- Produce workflow suggestions to increase efficiency and decrease duplication and file loss/misplacement

Methods: The Data Repository is comprised of a backend component and two cloud application user interfaces: (1) the storage and retrieval repository and (2) the team management module. The uploaded files are stored in a backend centralized file system within the repository and individual organizational units are defined by three data storage component s (i.e. drug, project, study). The type of the data storage component determines the directory template that is used to organize files; this directory template structure is automatically generated when a data storage component is created. The folder structure template is mapped to a permission matrix, which defines the user roles which can access and perform actions on files within a given data storage component at a given file path location. Relationship linking functionality was developed to allow data storage component items to display relationships defined by administrative users, to facilitate the identification of relationships between drugs, projects and studies. The team management module allows system administrative roles to manage the system and oversee data storage components, users, roles, and team assignments. Teams can be associated with one or more data storage component. Teams can include users from the same organization or disparate organizations, whilst retaining permission-based role collaboration within the Data Repository. Each user within a team is assigned a team role, which enables the user to perform specific actions. Actions can be described as functions that can be performed within the various data storage components. Users can upload and perform tasks on appropriate files on their assigned Drugs, Projects, and Studies. User actions are specific to their role and permissions and each user role has a pre-defined set of these actions that can be used. Version control using Git™ [1] was implemented to allow detailed tracking of file version and metadata changes, as well as actions performed. Import functionality allows administrative users to review and correct location and file metadata information in a Staging Area before allowing access to other users. Actions performed within the system are recorded in system logs for traceability, and authorized users may add comments to each file.

Results: The Data Repository is a cloud application with a user interface which allows users to manage and browse files and associated specific pharmacometric metadata within a pre-defined directory structure stored in a version control system. The Data Repository has a hierarchical structure to control organizational, team, and user access to shared data files. Users have assigned roles that enable specific actions unique to their roles and permissions

Conclusions: The Data Repository serves as a collaborative platform for knowledge accumulation. The Data Repository gives the repository owner the ability to control user access to shared data files through the use of teams and user roles. The Data Repository increases the efficiency of data curation and retrieval and increases the ease of communicating and sharing these results in a secure environment.

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S-02: *Sebastien Bihorel* Data exploration libraries in KIWI

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Objectives: Data exploration is critical to the success and efficiency of pharmacometric analyses by allowing the identification of key data patterns, guiding the modeling strategy, and supporting regulatory submissions. Creation of meaningful displays can be time-consuming and typically requires strong programming skills. The Explore and ExploreLive modules of the cloud-based KIWI platform[1] were created to automate the creation of data exploration plots and tables and designed to optimize the ease of use, quality of display, flexibility, interactivity, reproducibility, and traceability.

Methods: Both modules are graphical interfaces which fully integrate with existing KIWI modules and can simultaneously explore multiple datasets and output tables. All graphical and tabular displays are created with R.[2] Explore is a web module intended for the creation and permanent storage of report-quality tables and lattice-based plots.[3] R scripts are automatically generated and executed using the profile of settings selected in the graphical interface. All outputs are stored in a database and tied to a unique dataset identifier assuring traceability and reproducibility. Upon completion, displays are rendered within the Explore module. ExploreLive is a Shiny application intended for the live and non-permanent creation of tables and interactive ggplot2-based plots, and the execution of small-scale data analysis.[4,5] The ExploreLive application is remotely hosted and rendered in the user web browser. All displays are generated on the server side based upon the user-selected options and rendered in the application.

Results: Explore offers a widely customizable library of exploratory displays, including summary statistics tables, scatter and line plots, barcharts, boxplots, histograms, and pairwise matrix plots. For each type of display, users can create multiple profiles of settings that they can re-use across all projects initiated in the shared user environment. Custom settings are numerous and include data subsetting, variable selection, data stratification, layout, axis settings, summary statistics selection, etc. Execution of these custom profiles typically generates multiple displays which are automatically organized in a hierarchical tree format for convenient navigation and comparison across multiple data sources. Explore leverages the graphical standards and data formatting features established for model diagnostic plotting in the Visualize module, offering seamless visual integration in technical reports. ExploreLive is intended as a sandbox environment. It allows users to modify, merge, and subset data sources, create a large variety of interactive plots and tables, and perform linear regression, data binning, and survival analysis. Similar to Explore, the ExploreLive module offers a large number of custom options providing high interactivity for data manipulation and exploration. The Shiny architecture implements swift reactivity between user input changes and the update of the display rendered on screen. Interactive features allow users to click on plots and obtain relevant information about the data source.

Conclusions: Explore and ExploreLive naturally extend the functionality of the KIWI platform and provide powerful and user-friendly tools for data exploration. The library of displays provided by Explore enables busy scientists and those with no programming skills to quickly generate meaningful tables and plots to support their pharmacometric needs. By leveraging the infrastructure and features previously established, Explore maintains consistency and reproducibility in the design of tables and plots across projects and

between exploratory and model-diagnostic displays. ExploreLive offers a convenient environment for quick data exploration and investigation of data patterns.

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S-03: *Rikard Nordgren* Perl speaks NONMEM (PsN)

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PsN is an open source toolbox for population PK/PD model building using NONMEM. It has broad functionality ranging from results extraction to advanced computer-intensive statistical methods. PsN simplifies the organization of NONMEM output files, helps with starting jobs on different types of clusters (i.e. slurm, torque, sge and lsf) and can perform a cornucopia of different statistical methods, including: **benchmark** – combinatoric benchmarking of different NONMEM control stream settings, **bootstrap, cdd** – case deletion diagnostic to look for influential individuals, **frem** – full random effects modelling, **resmod** – residual modelling for quickly assessing appropriateness of structural [1] and residual error models [2], **scm** – stepwise covariate model, **simeval** – simulation evaluation diagnostics of outliers, **sir** – sampling importance resampling for parameter uncertainty assessment, **sse** – stochastic simulation and estimation and **vpc** – visual predictive check.

Updates to PsN since PAGE 2017 include a new tool, **qa**, which can be used to assess the quality of a model. **qa** uses "proxy models" (linearization [3] and residual error modelling [2]) to assess and highlight potential improvements to specific parts of a model, providing insights into the structural, variability and covariate components of a model. **qa** can also be used to identify influential individuals and outliers. The results of **qa** are presented in an automatically generated report. Another new tool, **transform**, can automatically add or transform variability terms in the model (ETAs) to Box-Cox or t-distributions, add interoccasion variability terms (IOV) to a parameter and convert omegas to full block form. **transform** also includes some more trivial transformations, such as automatically removing specific individuals and removing IIV or IOV separately from a model. **transform** is intended both as a help for manual model building but also to facilitate automation, via scripts, of some tedious model building tasks. In addition, the **vpc** tool can now create visual predictive check (VPC) plots for mixture models. One VPC plot will be generated for each mixture based on the MIXEST from NONMEM, or randomization from the individual probabilities in the phm-files [4]. Furthermore a new yaml formatted file is generated by all PsN runs containing metadata such as start and finish time, NONMEM and PsN versions used, command line, R package versions used etc. This simplifies programmatic extraction and reproducibility of runs. Finally, this year, updates have been made to **frem**, a tool for full random effects covariate modelling.

PsN can automatically generate plots for most of the different tools by adding the -rplots option. This automatically generates documents with, for example, visual predictive checks as part of the PsN output, without the need to manually run any R script. Many of these plots use functionality in the Xpose4 R package [5]. It is possible to customize the plots or replace them entirely by using custom R templates. These templates can either be plain R or R Markdown.

PsN is freely available at https://uupharmacometrics.github.io/PsN and the userguides for the different tools can be found at https://uupharmacometrics.github.io/PsN/docs.html

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S-04: *Tarjinder Sahota* NMproject: Tidy, Reproducible, Script Based NONMEM projects in RStudio. A Step Toward Pharmacometric Industrialisation.

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Objectives:

Knowledge management is the ability of an organisation to retain, reuse and share knowledge when/where it is needed. Have you ever spent time implementing model code that you later found out had already been implemented by one of your colleagues? Perhaps you missed that colleague's email or presentation. Have you ever had to continue a colleague's work but struggled to figure out what he/she did and in what order? Have you ever had trouble reproducing results you produced mere months ago because now there's a package/R version incompatibility? Have you ever had to repeat entire model development steps because of a small change to the initial dataset? We aim to develop a suite of R packages to overcome these challenges.

Methods:

Two R packages have been created:

TidyProject: Directory and code management.

NMproject: A light interface to NONMEM from R for script based model development (requires installation of NONMEM and Perl speaks NONMEM (PsN)).

Installing NMproject will install both packages. They will soon be released on the Comprehensive R Archive Network (CRAN), but are currently available on GitHub via the following R command: devtools::install_github("tsahota/NMproject"). NMproject can be configure for a wide variety of infrastructures.

Results:

AstraZeneca employees have successfully used NMproject to conduct NONMEM model development for over two years. A short summary of features of features is available on Youtube: https://www.youtube.com/watch?v=b7oBb6QZub8. Features include:

Tidy directory structure: Standardised, version controlled, directory structure for all NONMEM/R users. Functions to check your own adherence to best practices.

Run database: A hidden SQLite database monitors all runs, ensures new outputs don't overwrite existing outputs and enables easy creation of run histories.

Code library: An extensive library of templated control streams utilising best coding practices to reduce time spent coding NONMEM control streams, maximise stability and reduce errors. Create new templates for private use or for your organisation. Interface to search using keywords, tags, or raw text.

Private project library: Long term reproducibility and consistent running of R scripts between users. Store session information in case of catastrophic failure.

Script based model development: Code your model development process using end-to-end R scripts. Switch between interactive (for normal model development) and non-interactive mode (for sequencing multiple runs and post processing steps).

Shiny run monitor: Shiny GUI interface for run monitoring and results comparison.

Conclusions:

NMproject is a prototype of industrialised knowledge management for NONMEM and R users.