Tuesday June 10

18.30-20.00	**Registration at the Cruise Terminal**	
20.30-22.30	**Welcome reception at the Santísima Trinidad located in front of Hotel Melia**	

Wednesday June 11

08:00-08:45	**Registration**	
08:45-09:00	**Welcome and Introduction**	
09:00-10:20	**OrBiTo and Mechanistic absorption modelling**	*Chair: Leon Aarons and Panos Macheras*
09:00-09:40	*Amin Rostami-Hodjegan*	OrBiTo - translating mechanistic knowledge on absorption into predictive models
09:40-10:00	*Benjamin Guiastrennec*	Mechanism-based modelling of gastric emptying and bile release in response to caloric intake
10:00-10:20	*Andrés Olivares-Morales*	An in silico physiologically-based pharmacokinetic (PBPK) study of the impact of the drug release rate on oral absorption, gut wall metabolism and relative bioavailability
10:20-11:50	**Coffee break, Poster and Software session I**	
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter	
11:50-12:40	**Facilitating Modelling and Simulation**	*Chair: Charlotte Kloft*
11:50-12:10	*Kapil Gadkar*	Development of Virtual Population for a Quantitative Systems Pharmacology model
12:10-12:30	*Maciej Swat*	PharmML 1.0 – An Exchange Standard for Models in Pharmacometrics
12:30-12:40	*Marc Gastonguay*	Proposal for a Web-Based Open Pharmacometrics Curriculum
12:40-14:10	**Lunch**	
14:10-15:10	**Model-based individualisation**	*Chair: Nick Holford*
14:10-14:50	*Pierre Marquet*	Implementing model-based individualization in the clinic

14:50-15:10	*Núria Buil Bruna*	A step forward toward personalised medicine in oncology: Population modelling for the early prediction of disease progression using biomarkers
15:10-16:30	**Tea break, Poster and Software session II**	
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter	
16:30-17:50	**Drug/Disease modeling**	*Chair: Oscar Della Pasqua*
16:30-16:50	*Julia Korell*	Application of a model based longitudinal network meta-analysis of FEV1 in COPD trials in clinical drug development
16:50-17:10	*Sebastian Weber*	Bayesian Drug Disease Model with Stan - Using published longitudinal data summaries in population models
17:10-17:30	*Angelica Quartino*	An integrated natural disease progression model of nine cognitive and biomarker endpoints in patients with Alzheimer's Disease
17:30-17:50	*Yaming Hang*	Pharmacokinetic and Pharmacodynamic Analysis Longitudinal Gd-Enhanced Lesion Count in Subjects with Relapsing Remitting Multiple Sclerosis Treated with Peginterferon beta-1a

Thursday June 12		
08:45-10:05	**Lewis Sheiner Student Session**	*Chair: Emmanuelle Comets, Joachim Grevel and Panos Macheras*
08:45-09:10	*Thi Huyen Tram Nguyen*	Handling data below the quantification limit in viral kinetic modeling for model evaluation and prediction of treatment outcome
09:10-09:35	*Nikolaos Tsamandouras*	Development of population based approaches to describe the complex pharmacokinetics of simvastatin in different individuals. Bridging the gap between population and physiologically based pharmacokinetic modelling
09:35-10:00	*Mélanie Wilbaux*	A dynamic K-PD joint model for the kinetics of CTC (Circulating Tumor Cell) count and PSA concentration during treatment in metastatic castration-resistant prostate cancer
10.00-10.05	**Presentation of Lewis Sheiner student session awards**	
10:05-11:30	**Coffee break, Poster and Software session I**	
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter	
11:30-12:50	**Regulators and EFPIA initiatives for Modeling Informed Drug Discovery and Development (MID3)**	*Chair: Dinesh Dealwis and Marylore Chenel*
11:30-11:50	*Scott Marshall*	Proposed Modelling and Simulation good practices: Progress post EMA / EFPIA M&S workshop
11:50-12:15	*Terry Shepard*	How European Regulators are Facilitating the Use of Modelling and Simulation: MSWG History, Activity and Future
12:15-12:35	*Efthymios*	EMA qualification of novel methodologies: are we ready for M&S?

	Manolis	
12.35-12.50	**Panel discussion**	
12:50-14:15	**Lunch**	
14:15-15:15	**Regulators and EFPIA initiatives for Modeling Informed Drug Discovery and Development (MID3) continued**	*Chair: Mick Looby and Dinesh Dealwis*
14:15-14:40	*Bjoern Bornkamp*	The MCP-Mod methodology – A statistical methodology for dose-response modelling
14:40-15:15	*Vikram Sinha*	The role of MBDD in drug development - is it time to repaint the canvas?
15:15-16:40	**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	**Pharmacometric models for dose-finding and cost effectiveness**	*Chair: Lena Friberg*
16:40-17:00	*Camille Vong*	In silico comparison of MTD determination in a phase I dose-finding framework
17:00-17:20	*Coen van Hasselt*	Towards early integrated mechanism-based prediction of clinical outcome and cost-effectiveness in castration-resistant prostate cancer

Friday June 13

09:00-10:00	**Stuart Beal Methodology Session**	*Chair: France Mentré*
09:00-09:20	*Edouard Ollier*	Group comparison with fused lasso penalized likelihood: an alternative to test based methods
09:20-09:40	*Elin Svensson*	Prediction of pharmacokinetic interactions for drugs with a long half-life – evidence for the need of model-based analysis
09:40-10:00	*Yasunori Aoki*	Averaged Model Based Decision Making for Dose Selection Studies
10.00-10.05	**Preview of PAGE 2015**	
10:00-10:40	**Coffee break and Software session**	
10:50-12:10	**Modelling in oncology**	*Chair: René Bruno*
10:50-11:10	*Sharon Hori*	Modeling cancer blood biomarker dynamics in relation to tumor growth
11:10-11:30	*Rik de Greef*	Modeling of tumor size reduction patterns in advanced melanoma under treatment with MK-3475, a potent antibody against PD-1
11:30-11:50	*Pauline*	A mixed-effect modeling framework to personalize treatment of low-grade

	Mazzocco	glioma patients
11:50-12:10	*Nick Holford*	Power and Type 1 Error of Tumour Size Metrics Used to Predict Survival
12.10-12.20	**Closing remarks**	
12:20-12:40	**Audience Input for the PAGE 2015 Program**	

PAGE2014 Abstracts: Oral Program

Amin Rostami B-03 OrBiTo - translating mechanistic knowledge on absorption into predictive models

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OrBiTo is a new European project within the IMI programme in the area of oral biopharmaceutics tools that includes world leading scientists from nine European universities, one regulatory agency, one non-profit research organization, four SMEs together with scientists from twelve pharmaceutical companies.

The OrBiTo project will address key gaps in our knowledge of gastrointestinal (GI) drug absorption and deliver a framework for rational application of predictive biopharmaceutics tools for oral drug delivery. This will be achieved through novel prospective investigations to define new methodologies as well as refinement of existing tools.

Extensive validation of novel and existing biopharmaceutics tools will be performed using active pharmaceutical ingredient (API), formulations and supporting datasets from industry partners. A combination of high quality in vitro or in silico characterizations of API and formulations will be integrated into physiologically based in silico biopharmaceutics models capturing the full complexity of GI drug absorption. This approach gives an unparalleled opportunity to initiate a transformational change in industrial research and development to achieve model-based pharmaceutical product development in accordance with the Quality by Design concept. Benefits include an accelerated and more efficient drug candidate selection, formulation development process, particularly for challenging projects such as low solubility molecules (BCS II and IV), enhanced and modified-release formulations, as well as allowing optimization of clinical product performance for patient benefit. In addition, the tools emerging from OrBiTo are expected to significantly reduce demand for animal experiments in the future as well as reducing the number of human bioequivalence studies required to bridge formulations after manufacturing or composition changes.

Benjamin Guiastrennec B-04 Mechanism-based modelling of gastric emptying and bile release in response to caloric intake

Benjamin Guiastrennec (1), David P. Sonne (2,3), Oskar Alskär (1), Morten Hansen (2,3), Jonatan I. Bagger (2,3), Asger Lund (2,3), Jens F. Rehfeld (4), Mats O. Karlsson (1), Tina Vilsbøll (2), Filip K. Knop (2,3), Martin Bergstrand (1)

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Objectives: We aimed to establish a mechanism-based model for gastric emptying (GE), cholecystokinin (CCK) plasma concentrations and gallbladder (GB) emptying in response to caloric intake.

Methods: Data were gathered from 3 clinical studies with paracetamol absorption as a marker for GE, measurements of CCK plasma concentrations and ultrasound monitoring of the GB volume [1,2,3]. The studies included in total 33 healthy subjects and 33 type 2 diabetes patients. The studies featured paracetamol (1.5g) dissolved in: water (100mL), 25, 75 and 125g glucose solution (300mL), or isocaloric low, medium and high fat content liquid meal (350mL).

Previously published paracetamol population pharmacokinetic models [4,5] were modified to incorporate a feedback mechanism from the nutritional content in duodenum regulating the rate of GE. Prior information on glucose turnover in duodenum was taken from a model by Alskär et al [5]. GE was further described in terms of emptying of stomach volume (meal volume).

CCK turnover was modelled with two precursor indirect response models [6]. Release of CCK from the precursor pools was investigated as a function of nutritional content in duodenum and jejunum respectively. GB emptying was modelled with recirculation of bile from the small intestine to the GB via a chain of transit compartments. The effect of CCK or nutritional content on emptying of the GB compartment was investigated.

Results: Glucose in duodenum was found to have an inhibiting effect on GE following a sigmoidal Imax (IC_{50}=2.2g, Hill=3.1) relationship. Given the complex composition of the meals, the effect of low, medium and high fat meals on GE was estimated in glucose equivalent units. All meals were found to similarly inhibit GE, analogous to approximately 125g of glucose.

The typical dual peak profiles seen for the CCK plasma concentrations were successfully described by a model including release of a rapid half-life CCK (6.2min) and a slower half-life CCK (51min) stimulated by nutritional content in duodenum and jejunum respectively. Stimulation of GB emptying was best described by an E_{max} relationship driven by relative elevation of CCK levels.

Conclusions: An integrated model for GE, CCK plasma concentrations and GB emptying was developed and demonstrated to be predictive across a wide range of nutritional content of liquid meals. This could serve as a basis for improvements in both bottom-up and top-down approaches to describe oral absorption.

References:

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Potential Implications for Thyroid Function and Glucose Homeostasis. ADA 73 (2013) Abstr 2894-PO.
[2] Hansen M et al. Effect of Bile Acids on GLP-1 Secretion. ClinicalTrials.gov identifier NCT01666223.
[3] Bagger JI et al. Impaired Regulation of the Incretin Effect in Patients with Type 2 Diabetes. J Clin Endocrinol Metab (2011) 96(3): 737–745.
[4] Ogungbenro K et al. A Semi-mechanistic Gastric Emptying Model for the Population Pharmacokinetic Analysis of Orally Administered Acetaminophen in Critically Ill Patients. Pharm Res (2011) 28: 394–404.
[5] Alskär O et al. Modelling of glucose absorption. PAGE 22 (2013) Abstr 2897 [www.page-meeting.org/?abstract=2897].
[6] Sharma A, Ebling WF, Jusko WJ. Precursor-Dependent Indirect Pharmacodynamic Response Model for Tolerance and Rebound Phenomena. J. Pharm. Sci. (1998) 87(12): 1577-1584.

Andrés Olivares-Morales B-05 An in silico physiologically-based pharmacokinetic (PBPK) study of the impact of the drug release rate on oral absorption, gut wall metabolism and relative bioavailability

Andrés Olivares-Morales (1), Adam S. Darwich (1), Yoshiteru Kamiyama (1, 2), Leon Aarons (1) and Amin Rostami-Hodjegan (1, 3).
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Objectives: To investigate the impact of the drug release rate on oral drug absorption and CYP3A4-mediated gut wall metabolism and to identify the formulation and drug-specific factors associated with higher relative bioavailability observed for some controlled release (CR) formulations compared to their immediate release (IR) counterparts [1,2].

Methods:A systematic analysis was performed to assess the impact of formulation characteristics and drug-specific factors on oral bioavailability. A set of virtual compounds were generated by combinations of different values for drug-related parameters such as: aqueous solubility, human jejunal effective permeability (P_{eff}), maximal CYP3A4-mediated metabolic rate ($V_{max,\ CYP3A4}$), CYP3A4 affinity ($K_{m,\ CYP3A4}$) maximal P-gp-mediated efflux rate ($J_{max,\ P\text{-}gp}$) and P-gp affinity ($K_{m,\ P\text{-}gp}$). Five different release profiles were evaluated for each virtual compound, from fast (IR) to slow release (CR). Simulations were performed employing the "Advanced Dissolution Absorption and Metabolism (ADAM)" model within the Simcyp® Population-Based Simulator (v12) [3]. The results were analyzed for trends in fraction of the drug absorbed (f_a), fraction that escapes from first pass metabolism in the gut wall (F_G) and relative oral bioavailability (F_{rel}).

Results: In all the investigated scenarios the oral absorption (f_a) of CR formulations was lower as compared to the IR formulations. However, for highly permeable compounds that were CYP3A4 substrates, the reduction in absorption was compensated by an increase in the F_G, which was dependent on CYP3A4 affinity. In addition, BCS class 1 highly-cleared CYP3A4 substrates displayed up to 220% higher F_{rel} when formulated as CR compared to their IR formulations.

Conclusions: The results were consistent with a previous study on the colonic absorption of several drugs[4]. This study gives a mechanistic insight in to the processes involved in the absorption and first pass metabolism in the distal regions of the GI tract. The decreased absorption in the distal regions of the GI tract can be compensated by a reduction of the intestinal first pass metabolism, presumably due to the distribution of the CYP3A enzymes along the gut wall, where the abundance in to the distal regions is decreased compared to that in the upper regions[5]. This information can be employed during the formulation development in order to maximize drug absorption, especially for CYP3A4 substrates.

References:
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[5] Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, Perkins JD, Thummel KE. Characterization of Interintestinal and Intraintestinal Variations in Human CYP3A-Dependent Metabolism. J Pharmacol Exp Ther 1997; 283: 1552-62.

Kapil Gadkar B-07 Development of Virtual Population for a Quantitative Systems Pharmacology model

Kapil Gadkar (1), Saroja Ramanujan (1)
(1) Development Sciences, Genentech

Objectives: Quantitative systems pharmacology (QSP) is an emerging discipline that focuses on analysis of the dynamic interactions between drug(s) and biological systems to understand the behavior of the system as a whole, as opposed to isolated behavior of individual components (van der Graaf & Benson 2011). Given the integrative nature of the approach, the corresponding mathematical and computational models frequently incorporate a wide range of data from in-vitro, preclinical, and clinical studies. This work describes a 4-stage approach for virtual population development suited for QSP models.

Methods: The first step involves identification and exploration of model parameters to generate numerous potential virtual patients; this exploration is based typically on in-vitro and preclinical data. In the second stage, simulations of the potential virtual patients are compared to clinical data of interest to select "relevant" virtual subjects. In the third stage, the selected virtual patients are validated against clinical data not used in the selection stage. A fourth model refinement stage is required for the scenario in which the validation criteria are not met in stage 3. Refinement could involve modifications of the model structure to include additional details of the biological process or could be limited to additional parameter exploration and virtual patient generation. The virtual population developed through this process represents both potential variability in the underlying biology and clinical variability observed in the "real" population. Each patient in the virtual population is assigned a prevalence weight [1], such that the weighted virtual population reproduces key statistical properties of clinical population data. These properties could include means and distributions of clinical measurements and readouts at baseline and/or in response to therapies, as well as correlations between multiple measurements. Thus, the prevalence weight of each individual virtual patient represents its contribution to statistical properties of the virtual population.

Results: The virtual population development approach is described for a QSP model of LDL cholesterol lowering by anti-PCK9.

Conclusions: The above systematic methodology of data integration and variability exploration into a virtual population is well suited for in-silico research in QSP models.

References

[1] Schmidt, B. J., F. P. Casey, et al. (2013). "Alternate virtual populations elucidate the type I interferon signature predictive of the response to rituximab in rheumatoid arthritis." BMC Bioinformatics **14**: 221

Maciej Swat B-08 PharmML 1.0 - An Exchange Standard for Models in Pharmacometrics

Maciej J Swat (1), Sarala Wimalaratne (1), Niels Rode Kristensen (2)
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Objectives: The lack of a common standard for exchange of models between different software tools used in population pharmacokinetics/ pharmacodynamics (e.g. NONMEM, Monolix and BUGS) has been a longstanding problem in the field. PharmML is intended to become such standard. It is being developed by the DDMoRe consortium, a European Innovative Medicines Initiative (IMI) project.

Methods: PharmML has been developed based on requirements provided by the DDMoRe community, including numerous academic and EFPIA partners, in the form of use cases for various estimation and simulation tasks (encoded in languages such as NMTRAN and MLXTRAN) and documents outlining the mathematical/statistical background ([1], [2]). The standard is developed as an XML schema definition, and existing standards are reused where possible (e.g. UncertML is used to encode variability/uncertainty).

Results: The current version supports Maximum Likelihood Maximization and Bayesian methods for models used in analysis of continuous/discrete longitudinal population PK/PD data with

- Structural models defined as a system of ordinary differential equation (ODE) and/or as algebraic equations.
- A flexible parameter model allowing for implementation of arbitrary parameter type used in the majority of models with discrete or continuous covariates.
- A nested hierarchical variability model capable of expressing very complex variability structures.
- An observation model supporting untransformed or transformed continuous, categorical, count or time-to-event data.
- A trial design model, based on a CDISC standard ([3]), allowing for definition of common designs such as parallel or crossover with virtually any administration type.
- Typical modelling steps such as estimation or simulation based on inline or externalised experimental data sets.

Conclusions: The current PharmML specification allows already for the implementation of standard pharmacometric models and is a solid base for further development of PharmML over the remaining two years of the project. Subsequent releases will support delay and stochastic differential equations, optimal experimental design, etc.

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[2] Keizer, R. and Karlsson, M. (2011). Stochastic models. Technical report, Uppsala Pharmacometrics Research Group.
[3] CDISC SDM-XML Technical Committee (2011). CDISC Study Design Model in XML (SDM-XML), Version 1.0. Technical report.

Marc Gastonguay B-09 Proposal for a Web-Based Open Pharmacometrics Curriculum

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Objectives: Given the small number of formal academic training programs and associated faculty, resource sharing and collaboration in pharmacometrics (PM) training are critical to the continued development of the discipline [1]. The objectives of this work were: 1). to quantify the extent and intensity of global interest in an open pharmacometrics curriculum (OPC), and 2). to identify additional web-based resources that could potentially make up a complete OPC.

Methods: Six semester-long courses on various PM-specific topics were developed, with audio/video, recordings and supporting example files. The resulting 126 videos were made open and freely available by posting on a YouTube channel [2], with simultaneous announcement on the NMusers discussion group. Usage data from Google web analytics were collected over a 4-month period. Web searches were performed to identify additional open courses, relevant to an OPC.

Results: Over the 4-month period, lectures were viewed 15,240 times, from individuals in 76 different countries, for a total of 129,375 minutes watched. A pattern of short views in the initial week of availability, was followed by a pattern of longer view times (averaging approximately 20 min. each), which was sustained over the time studied. Views primarily originated from computers (88%), followed by tablets (7.6%), and mobile phones (4.4%). 200 individuals subscribed to the channel. Additional freely available, open web courses were identified to supplement the OPC, in topic areas such as: math, pharmacology, programming languages, and statistics.

Conclusions: Results reveal a strong global interest in an OPC, with evidence of in-depth study of the materials, and ready availability of additional training content. Given the positive initial results, future efforts will focus on building a complete OPC.

References:
[1] Barrett JS, Fossler MJ, Cadieu KD, Gastonguay MR. Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. J Clin Pharmacol. 2008 May;48(5):632-49.
[2] http://www.youtube.com/user/metruminst

Pierre Marquet B-11 Model-based personalized medicine in transplantation

Pierre Marquet
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Personalized medicine encompasses at least precision diagnostics, targeted therapies (when available) or personalized treatment, as well as personalized patient care.

Anti-rejection therapy in organ transplantation has long been a privileged application field for the development of medicine personalization, owing to the narrow therapeutic margin of most immunosuppressants (IS), the unavoidable pharmacokinetic (PK) interactions between the drugs associated in the usual therapeutic regimens and the unescapable long term toxicity of most IS.

The variability in the therapeutic and toxic effects of immunosuppressants obviously has pharmacokinetic and pharmacodynamic (PD) origins, both with genetic and environmental causes. Over the last two decades, patient care has been improved by using PK monitoring in order to identify the sources of, and compensate as much as possible for, the variability of IS drugs therapeutic and side effects. This has involved population pharmacokinetic (popPK) analysis and modelling, Bayesian estimators of exposure and dose adjustment tools (some of which have been made accessible through websites).

At the same time, the IS pharmacogenetic-pharmacokinetic relationships have been explored. Among the many polymorphisms in genes coding for drug metabolizing enzymes or efflux transporters explored, only a few have shown a strong enough impact on PK to be taken into account for *a priori* (before the first dose) or *a posteriori* (based on measured concentrations) dose adjustment, and/or have been proposed as covariates in popPK models. The influence of pharmacogenetics on drug targets has been studied less so far, although it holds promise for a better understanding of the sources of pharmacodynamic variability.

The pharmacodynamics of these drugs, such as the measurement of the calcineurin pathway activity, IMPDH activity, leucocyte proliferation or activation in patients' blood, have been explored so as to estimate their variability, investigate their sources and evaluate their potential use for treatment personalization. This is also a prerequisite for useful PK/PD modelling.

Finally, biomarkers are being searched to anticipate and improve the diagnosis of renal graft injuries and of graft failure. Ultimately, they may be usefully implemented in predictive models of graft function or survival.

In summary, a more global, pharmacogenetic-pharmacokinetic-pharmacodynamic-clinical approach might help to significantly improve individual treatment strategies in the long term, including informed and iterative selection of IS drugs and their dose adjustment, i.e. true treatment personalization. This will obviously require sophisticated models able to integrate many risk factors of different types and predict patient and graft outcome.

Núria Buil Bruna B-12 A step forward toward personalised medicine in oncology: Population modelling for the early prediction of disease progression using biomarkers

(1) Núria Buil-Bruna, (2) José-María López-Picazo, (3) Marta Moreno-Jiménez, (2) Salvador Martín-Algarra, (4)* Benjamin Ribba and (1)* Iñaki F. Trocóniz

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** These authors share the senior authorship of this work*

Objectives: Development of individualised therapies poses a major challenge in oncology. Significant hurdles to overcome include better disease monitoring and early prediction of clinical outcome. We propose a population modelling framework that relates circulating biomarkers in plasma, easily obtained from patients, to tumour progression levels assessed by imaging computed tomography (CT) scans (i.e., Response Evaluation Criteria in Solid Tumors (RECIST) (1) categories). We apply this modelling and prediction strategy to small cell lung cancer (SCLC) patients.

Methods: First, we developed a biomarker model using 369 lactate dehydrogenase (LDH) and 152 neuron specific enolase (NSE) concentrations from medical records of 60 patients. The model comprised two indirect response models for LDH and NSE, where biomarker levels were driven by an underlying latent variable ("disease level") representing (unobserved) tumour size dynamics. Second, based on 215 RECIST categories, we developed a logistic regression model which related the change in the unobserved disease variable to a probability of disease progression [P(DP)]. We then used MCMC Bayesian analysis to obtain the full uncertainty distribution of individual future P(DP). Finally, we determined the minimal number of individual biomarker concentrations (earliest interim time point) required to obtain accurate future predictions of P(DP).

Results: The biomarker model successfully described LDH and NSE dynamics. Predictive checks on the proportion of individuals with disease progression obtained with the combined model showed good model performance. Earlier predictions were associated with less individual data and therefore higher uncertainty. For the end of therapy CT scan, the model achieved accurate prediction of P(DP) in most of the patients before the last scheduled chemotherapy cycle providing a possibility for early transfer to second line treatment in patients where a high P(DP) is predicted. For the follow-up CT scans, accurate predictions were achieved at least 5 weeks prior to the scheduled time.

Conclusions: We have developed a model for LDH and NSE in SCLC patients which allowed estimation of underlying disease levels. We have extended the model to predict P(DP) using the predicted change in latent disease level, showing that the use of the population model enables accurate individual predictions of P(DP) prior to tumour response assessments.

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(2) Buil-Bruna N, López-Picazo JM, Moreno-Jiménez M, Martín-Algarra S, Ribba B, Trocóniz IF. A population pharmacodynamic model for lactate dehydrogenase and neuronal specific enolase to predict tumor progression in small cell lung cancer patients. The AAPS Journal 2014; Advance online publication. doi:

10.1208/s12248-014-9600-

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Julia Korell B-14 Application of a model based longitudinal network meta-analysis of FEV1 in COPD trials in clinical drug development

Julia Korell (1), Steven W. Martin (2), Mats O. Karlsson (1), Jakob Ribbing (1,3)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden, (2) Pfizer Inc, Cambridge, MA, USA, (3) Pfizer AB, Sollentuna, Sweden

Objectives: Efficacy benchmarking is an important decision making component in clinical drug development. Comparative effectiveness determines ranking and pricing among alternative treatments in many countries. In chronic obstructive pulmonary disease (COPD), the forced expiratory volume in 1 second (FEV1) is used to assess lung function [1], and serves as biomarker for dose selection [2]. A model based meta-analysis of literature data on FEV1 in COPD can facilitate this process.

Methods: Randomized COPD maintenance trials on long-acting bronchodilators (BD) and anti-inflammatory (AI) treatments published until July 2013 were identified from literature. Suitable summary level FEV1 data, treatment information and covariates were extracted. The literature data was analysed using NONMEM 7.2 by expanding and revising a previously developed database and FEV1 model [3].

Based on the final meta-model, comparative effectiveness among the treatments was assessed using log-likelihood profiling (LLP). The LLPs were set up to assess uncertainty in the relative efficacies, i.e. the efficacy of compound A over the efficacy of compound B for all contrasts.

Results: In total, 142 studies were included, comprising 106,422 subjects who received 19 compounds (11 BD, 8 AI) in 105 treatment combinations across 419 study arms. 1982 FEV1 observations were available for analysis, each representing the mean FEV1 for a treatment arm at a specific time point.

The final model included baseline, disease progression, placebo effect, and drug effects for all 19 compounds. Dose-response was identifiable for 10 compounds. Time course for on/offset of drug effects were included where information was available. Drug-drug interactions and the effect of concomitant background COPD treatment were also accounted for.

As the NONMEM covariance matrix was unreliable and non-parametric bootstrapping was unsuitable, sampling-importance resampling [4] was used to obtain parameter uncertainty, which allowed for asymmetric confidence intervals.

Comparative effectiveness among the BD treatments showed superiority of once-daily and novel BD over the established twice-daily BD, salmeterol and formoterol. Among the AI treatments, roflumilast showed the highest efficacy.

Conclusions: The FEV1 meta-model can serve as a tool for assessing comparative effectiveness across different compounds. It also provides FEV1 predictions for the development of a meta-model linking FEV1 with exacerbation rate in COPD.

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Sebastian Weber B-15 Bayesian Drug Disease Model with Stan - Using published longitudinal data summaries in population models

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Objectives: Model based comparison of an in-house drug to a within class registered drug is critical during drug development. This is often challenged by the need for (i) a complex drug disease model to describe the drug effect over time and (ii) the lack of patient level data of other compounds in the landscape. As an example, a turn-over K-PD model for best corrected visual acuity (BCVA) in wet age-related macular degeneration (AMD) patients is considered. This modelling effort is not only to describe ranibizumab BCVA time profile, but also to evaluate the drug disease model of aflibercept for which only published summary data from the two phase III studies VIEW 1+2 [2] are available. In this presentation we show how a Bayesian framework can resolve challenges (i) and (ii).

Methods: To demonstrate the approach, results are shown based on a sparse in-house data set with about 1000 patients. The patient population are wet AMD who received either sham injection, 0.3 mg or 0.5 mg ranibizumab as an intra-vitreous injection, dosing frequencies were monthly for the first 3 months and continued with a monthly or every 3 months schedule over a year. BCVA was assessed monthly. Bayesian analysis was performed with an extended version of Stan 2.2.0 [3]. A variant of sample importance resampling (SIR) is used to update the model parameters with VIEW1+2 summary data.

Results: A turn-over model was used to describe the patient natural disease progression and the patients were started at baseline in a non-steady state. The drug effect was modelled as a stimulation of Kin. As the initial response to the drug was observed to be rapid, a time-varying Emax function was used. To achieve a stable model fit informative priors on the natural disease progression parameters (i.e. Kin and Kout) and weakly informative priors for drug related parameters, that is Emax and EC50, were used. The final model described the in house data well and resulted in good convergence properties. The SIR procedure allowed the inclusion of the longitudinal summary data and enabled the estimation of EMAX and EC50 for aflibercept.

Conclusions: The Bayesian approach with weakly/informative priors was essential to improve computing efficiency and enabled fast convergence. Key for this achievement was the extended version of Stan with an ODE solver. This Bayesian method coupled with SIR algorithm enabled us to overcome computational challenges and to include summary level longitudinal data in the model parameter estimation for aflibercept.

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Angelica Quartino B-16 An integrated natural disease progression model of nine cognitive and biomarker endpoints in patients with Alzheimer's Disease

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Objectives: Progression in Alzheimer's Disease (AD) manifests as changes in multiple biomarker, cognitive, and functional endpoints. The aim is to establish a natural disease progression model integrating multiple endpoints in patients with AD.

Methods: This analysis included 298 mild AD patients (baseline MMSE of 20-26) from the Alzheimer's Disease Neuroimaging Initiative study [1]. Longitudinal changes up to 3 years in the following nine endpoints were modeled: the 6 items of the CDR scale, ADAS-cog 12, hippocampal and ventricular volumes. The model for AD patients was based on a previous disease model for mild cognitive impaired patients [2] and fitted to the data using OpenBUGS v. 3.2.2.

Results: The developed model for mild AD patients linked the nine endpoints via a latent "disease status" variable that evolves linearly over time according to patient-specific rates, controlled by APOE4 status and baseline MMSE. The model correctly identifies healthier patients with slower progression rates with an increase of baseline MMSE, and more rapid disease progression in APoE4 positive patients. Residual likelihoods were best described by multinomial for CDR items; lognormal for hippocampal and ventricular volumes; and beta distributed for ADAS-cog (as when modeled in isolation [3]).

Simulations using the model resulted in relative changes in the natural disease progression over two years, with 90% credible intervals, as: ADAS-cog, 42.3 [35.9 – 49.9]%; CDR-sum, 93.3 [81.0 – 107.8]%; hippocampal volume, -7.6 [-8.8 – -6.6]%; and ventricular volume as 24.0 [21.4 – 26.9]%. These predictions are consistent with observed two year rates of progression in these patients; 38.5% in ADAS-cog, 85.2% in CDR sum of boxes, -7.8% in hippocampal volume, and 23.0% in ventricular volume, confirming the adequacy of the model.

Conclusions: We developed an integrated disease progression model, which quantifies the interaction between nine clinical and biomarker endpoints and covariates relevant to AD. Such models, compared to previous single endpoint disease models for AD, may provide greater insight of the impact of patient covariates and drug effect on disease as well as the sensitivity of the different endpoints in subpopulations. The model also permits trial simulation of multiple endpoints with an appropriate joint distribution; useful when multi-endpoint decision criteria are envisioned for analysis.

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Yaming Hang B-17 Pharmacokinetic and Pharmacodynamic Analysis of Longitudinal Gd-Enhanced Lesion Count in Subjects with Relapsing Remitting Multiple Sclerosis Treated with Peginterferon beta-1a

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Objectives: To develop a pharmacokinetic (PK) and pharmacodynamic (PD) model to assess the effect of monthly exposure of peginterferon beta-1a (PEGIFN) on the reduction of Gd-Enhanced lesion count over time in patients with Relapsing Remitting Multiple Sclerosis (RRMS).

Methods: PK and Gd-Enhanced lesion count data were obtained from a double blind placebo-controlled Phase III study with RRMS patients (n=1512), where Placebo, PEGIFN 125 µg subcutaneous every 2 (Q2W) or 4 (Q4W) week dosing regimens were evaluated. A population PK model was developed based on both intensive and sparse samples of serum concentrations collected in this study. Poisson and Negative Binomial distributions were explored to describe the relationship between monthly cumulative area-under-concentration-time-curve (AUC) and Gd-Enhanced lesion count collected at Weeks 0, 24, 48 and 96. A variety of models were evaluated: Marginal model, Mixed Effect model with Single Population, Mixture models with two or three subpopulations. The effect of AUC on mean lesion count was described by a log-linear form. The Laplacian approximation method in NONMEM V7.2.0 [1,2] was used for parameter estimation.

Results: The disposition of PEGIFN was well described by a one-compartment linear model with a first-order absorption rate. A Two-population Mixture model with Negative Binomial distribution fits the exposure-response data well. Due to a significant proportion of subjects who had no Gd-Enhanced lesion detected at all visits, the subpopulation with less activity in Gd-Enhanced lesion is assumed to have a degenerative statistical distribution of mean baseline λ (estimate 0.546). The dispersion parameter for this group is 44.6. In the other subpopulation with more activity in Gd-Enhanced lesion, baseline λ is estimated to have a mean of 1.62 and 112% cv for inter-subject variation. The dispersion parameter for this group is estimated to be 0.452. Estimated probability for the low Gd-Enhanced lesion activity group is 59.3%. The estimated slope of AUC effect on log(λ) is -0.026. The latter suggests that at steady state, λ is approximately reduced by 64% and 87% from the baseline at the mean AUC value of the Q4W and Q2W groups (39.6 and 77.3 ng/mL*hr respectively).

Conclusions: The exposure-response model suggests that greater PEGIFN exposure in the Q2W group resulted in greater Gd-Enhanced lesion count reduction and explains the enhanced efficacy observed for the Q2W group, as compared to the Q4W group.

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Thi Huyen Tram Nguyen C-01 Handling data below the quantification limit in viral kinetic modeling for model evaluation and prediction of treatment outcome

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Introduction

Viral kinetic (VK) models have provided many insights into viral infection with various viruses, such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV). They allow evaluating the mechanism of action and effectiveness of antiviral agents [1–3]. The understanding of virologic response determinants can be improved by including pharmacokinetic (PK) information [4]. VK model can also be used to predict individual treatment outcome basing on early responses in order to optimize the duration of anti-HCV treatment [5]. One common problem in VK modeling is data below the quantification limit (BQL), which become more and more frequent with new effective treatments. These data can be handled with several estimation methods [6–8], but how they impact model evaluation and treatment response prediction and how to properly handle them in these steps is still a question. Most of the current diagnostic tools, including prediction discrepancies (pd) and normalized prediction distribution errors (npde), do not take into account BQL data.

Objectives

1) Extend two evaluation metrics, pd and npde, to handle BQL data.

2) Build a VK model using PK data to characterize virologic response to alisporivir (ALV) and pegylated interferon (pegIFN) given alone or in combination then evaluate this PKVK model with the new npde.

3) Evaluate the impact of BQL data, design and a priori information of population parameters on individual parameter estimates and treatment outcome prediction.

Methods

1) Pd/npde belong to the family of simulation-based evaluation metrics. They were developed in our group and implemented in an R package by Comets et al. to evaluate nonlinear mixed effect models [9,10]. Pd are computed as the quantile of observations in their predictive distribution obtained by simulation [10]. Npde are pd calculated from decorrelated observed and simulated data to handle within subjects correlations [11]. We developed a method to handle BQL data. First we evaluated the probability for an observation to be BQL (pBQL) from its predictive distribution. Its pd is then drawn randomly from a uniform distribution [0;pBQL]. To compute npde, BQL data are imputed from their pd drawn previously and the predictive distribution. The same imputation is performed for simulated data. Npde are then computed as usual from imputed datasets. The extended pd/npde were compared with naïve methods that omit BQL data. These methods were evaluated on a bi-exponential model for HIV infection, using graphic evaluation, type I errors and powers of 4 statistical tests, calculated from 1000 simulations under different scenarios [12].

2) ALV is a cyclophilin inhibitor with potent anti-HCV activity [13]. We estimated the effectiveness of ALV and pegIFN in 88 patients infected with HCV genotypes (G) 1-4 treated for 4 weeks with 3 doses of ALV ± pegIFN (phase 2 study DEB-025-203). First, we analyzed the PK of both drugs then used PK predictions as driving functions for the VK model. The PKVK model was evaluated with the new npde. We used this model to predict treatment response (%BQL data and cure rate (SVR)) for three ALV-containing treatment arms of the phase 2 study VITAL-1 [14]. Virus eradication (SVR) was assumed if the infected cells become lower than $10^{-4.2}$IU/mL under treatment [15]. BQL data were handled with SAEM in MONOLIX 4.2.2.

3) Individual treatment outcome can be predicted from early VK data, which may contain many BQL data. To study the use of VK data to predict individual response and factors influencing the prediction, we simulated VK data and SVR of 1000 HCV G2/3 patients treated with pegIFN/Ribavirin for 24 weeks, considering 4 nested designs with different sampling time and duration. We estimated individual parameters (infection rate β, infected cells' loss rate δ, virion clearance c and treatment efficacy ε) with Bayesian method by fixing population parameters at 3 sets of *a priori* information (true model with simulation parameters; false model $M_{\delta\varepsilon}$ with δ and ε of G1 patients; false model M_{β} with a modified β). Data simulated below 45 IU/mL were considered to be BQL [16].

Results

1) In model evaluation, ignoring BQL data resulted in biased and uninformative diagnostic plots, which were much improved with our proposed method. In presence of BQL data, type I errors obtained with naïve approach were much higher than 5%. With new metrics, type I errors were slightly higher than 5% only in scenarios with high interindividual variability but remained much lower than those obtained with naïve approach. Powers to detect model misspecifications with new npde were satisfactory in most cases but decreased when BQL data proportion increased [12]. These extensions as well as many other graphic options were implemented in npde package (version 2.0) for R, released on October 2012 [www.npde.biostat.fr]

2) In the analysis of PKVK data of patients treated by ALV ± pegIFN, a model assuming additive effect of both ALV and pegIFN in blocking viral production characterized viral loads with satisfactory plots of new npde. HCV genotype was found to significantly affect pegIFN effectiveness and infected cells' loss rate. ALV's effectiveness was not significantly different across GT and was higher (~90%) at doses ≥600 mg QD. Most of the observed responses in VITAL-1, where ALV was given at doses different from those observed in our study, were included in the 95% prediction intervals provided by the model.

3) In the simulation for Bayesian estimation, precise estimation of individual parameters and treatment outcome was obtained with only 6 data points in the 1st month of treatment. This remained valid even though wrong *a priori* population parameters were set as long as the parameters were identifiable (δ, ε) and BQL data were properly handled. False *a priori* information on estimable parameters (δ, ε) could lead to severe estimation/prediction errors if BQL data were omitted. However, taking into account BQL data did not improved estimation/prediction errors if false *a priori* information for poorly identifiable parameter (β) was used [16].

Conclusions

We proposed a method to extend pd/npde to take into account BQL data. The new metrics show better behaviors than naive methods that omit BQL data in evaluation and were implemented in the package npde 2.0. They were used to evaluate the PKVK model developed to analyze a phase 2 study of ALV where BQL data represented 27.6% of viral loads. The PKVK model was able to describe the observed data and provide reasonable predictions for virologic responses. Bayesian estimation of individual VK parameters can give precise prediction of treatment outcome from only few early responses, provided that BQL data are correctly handled and correct *a priori* information is available. These results highlighted the possibility of

using VK models to evaluate treatment effect, to predict treatment response, to support future clinical trials and to individualize therapy when BQL data are correctly handled.

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Nikolaos Tsamandouras C-02 Development of population based approaches to describe the complex pharmacokinetics of simvastatin in different individuals. Bridging the gap between population and physiologically based pharmacokinetic modelling.

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Objectives: Simvastatin (SV) is a prodrug with complex pharmacokinetics (PK) due to the interconversion between the parent drug and its main active metabolite, simvastatin acid (SVA) [1, 2]. Both SV and SVA are subject to drug-drug interactions (DDIs) [3] and are affected by genetic variation in several enzyme/transporter proteins relevant for their disposition [4-7]. The most serious adverse effect of SV is related to skeletal muscle and it can range from myalgia to myopathy and ultimately to the rare but potentially life-threatening rhabdomyolysis [4, 8]. Simvastatin-induced myotoxicity is a concentration-dependent adverse effect which is at least partly of a pharmacokinetic origin [9]. However, our understanding regarding the complex SV/SVA PK and especially their variability in the population is very limited.

This work aims to develop a joint population SV/SVA pharmacokinetic model that incorporates the effects of multiple genetic polymorphisms and clinical/demographic characteristics. Besides that, it also aims to provide a practical example of a covariate analysis where several genetic polymorphisms are tested and the degree of correlation between them through linkage disequilibrium has to be considered [10, 11].

In parallel, this work aims to develop an alternative much more complex but mechanistic population SV/SVA pharmacokinetic model. Such a model has the advantage that it can provide predictions not only for concentrations in plasma, but also in the clinically relevant tissues of muscle (toxicity) and liver (efficacy), while also it allows extrapolation outside the studied conditions. We have recently discussed the various methodological issues related with parameter estimation in such complex models [12]. Therefore, in this work we aim to also explore further methodological aspects such as: incorporation of population variability in system-related parameters which are subject to certain physiological constraints; parameter estimation with the aid of prior distributions; and application of different estimation algorithms.

Methods: SV/SVA plasma concentrations, demographic/clinical data and genotypes for 18 genetic variants were collected from 74 individuals and analyzed with NONMEM 7.2 in order to develop the population pharmacokinetic-pharmacogenetic model [13]. Several structural empirical parent-metabolite pharmacokinetic models were evaluated. Covariate selection was performed using a stepwise forward inclusion – backward elimination process that also examines the degree of linkage disequilibrium between correlated SNPs upon inclusion in each step. Finally the developed model was also used to identify individuals harbouring genetic and other clinical/demographic risk factor combinations that can be associated with clinically important increases on SV/SVA plasma exposure.

For the development of the complex mechanistic pharmacokinetic model, rich SV/SVA plasma concentration data (34 healthy volunteers) were simultaneously analysed with NONMEM 7.2. Additional rich plasma concentration data (28 healthy volunteers) were used for external validation of the model [14].

The implemented mechanistic model has a complex compartmental structure (presented in an earlier version of this work [15]) that allows interconversion between SV and SVA in different tissues. Prior information for model parameters and (when available) their variability was extracted from physiology, *in vitro* experiments and *in silico* methods in order to construct appropriate prior distributions. Variability in system related parameters was incorporated not only by linking them with several well-defined physiological covariates (e.g. body weight), but also by the use of random inter-individual variability terms. Therefore, a generalisation of the logit-normal distribution was applied to constrain some of the system parameters within their physiological range (e.g. gastric residence time) and a multivariate logistic normal distribution was applied on compositional parameters for which the physiological constraints apply on their joint distribution (e.g. fractions of cardiac output that reaches each tissue). The prior functionality in NONMEM [16, 17] was used to integrate prior information with the information from the clinical data and obtain maximum a posteriori (MAP) parameter estimates under the first order conditional estimation method with interaction (FOCE-I) and importance sampling assisted by mode a posteriori (IMPMAP) methods [18]. The developed model was finally employed to simulate concentration profiles in plasma, liver and muscle and investigate the impact of polymorphisms and a range of DDIs (clarithromycin, diltiazem, erythromycin, itraconazole).

Results: The empirical model that best described the data included a two- and a one-compartment disposition model for SV and SVA respectively. Age, weight, Japanese ethnicity and 7 genetic polymorphisms, rs4149056 (*SLCO1B1*), rs776746 (*CYP3A5*), rs12422149 (*SLCO2B1*), rs2231142 (*ABCG2*), rs4148162 (*ABCG2*), rs4253728 (*PPARA*) and rs35599367 (*CYP3A4*), were identified to significantly affect model parameters. The present work highlighted specific characteristics associated with altered SV/SVA PK and subsequently myopathy cases which cannot be solely attributed to a single genotype. Extensive results of this pharmacogenetic analysis are reported in [13].

The complex mechanistic model provided a good fit to the plasma SV/SVA concentration data and their variability. The incorporation of priors allowed precise estimation of model parameters without neglecting the random variability in key system and drug related parameters and the uncertainty [19] on the results of *in vitro* experiments or *in silico* predictions that are used to inform them. The FOCE-I and IMPMAP estimates were comparable, with the latter method (parallelised) showing significantly reduced computation times for convergence, similarly to previous studies with complex mechanistic models [20-22]. Simulations with the developed model using reduced SVA hepatic uptake (mimicking a *SLCO1B1* polymorphism) recovered the reported increase in exposure of SVA in plasma [5]; comparable increased fold-exposure was simulated in the muscle, consistent with the risk of toxicity in this tissue; whereas impact on liver exposure was minimal. In addition the developed model successfully predicted the effect of a range of DDIs on the PK of both SV and SVA.

Conclusions: The population based approaches developed in this work overall provide further insight into the PK of simvastatin and the related population variability. These approaches can be of significant clinical application due to the widespread use of simvastatin and the clinical burden of muscle toxicity. In addition the present work illustrates the feasibility of combining traditional PBPK with population approaches and information from clinical data in order to develop mechanistically sound population models with clinical relevance.

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Mélanie Wilbaux C-03 A dynamic K-PD joint model for the kinetics of CTC (Circulating Tumor Cell) count and PSA concentration during treatment in metastatic castration-resistant prostate cancer

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Objectives:

Prostate cancer is one of the most common cancers and the second leading cause of death. The PSA (Prostate-Specific Antigen) is a serum tumor marker currently used to evaluate treatment effect in prostate cancer; however its validity remains controversial. Therefore new markers are emerging, such as the count of Circulating Tumor Cells (CTCs), measured as the number of cells per sample of 7.5mL blood (aliquot). CTCs are tumor cells that have been released into blood and potentially prone to the development of new metastases. De Bono et al. reported that patients with a baseline CTC count greater or equal to 5 had a shorter survival than patients with a baseline CTC count lower than 5 [1]. They also showed that CTC count (< 5 or ≥5 per aliquot) was a better predictor of survival than PSA decrease (of 30% or 50%). As a consequence, the Food and Drug Administration (FDA) approved the use of CTC counts in the evaluation of metastatic castration-resistant prostate cancer (CRPC) p atients. The kinetics of CTC and their relationships with other markers such as PSA and tumor size need to be addressed.

The main objective of the present study was to quantify the dynamic relationships between the kinetics of PSA and CTC count during treatment in metastatic CRPC patients, linked by a latent variable.

Methods:

Patients:

The data from 224 patients, enrolled in IMMC38 trial meant to assess the relationships between categorized CTC count (-1[0–17800], were observed at different time-points along treatment. A median of 5 CTC and 5 PSA values were available per subject until 6 months after treatment initiation. Different types of kinetic profiles were observed, some with parallel PSA and CTC kinetics, others with faster or slower CTC kinetics compared to PSA kinetics.

Model:

A semi-mechanistic model was built to describe CTC count and PSA kinetics during treatment in CRPC patients. The model required to consider 4 levels of complexity:

1) The kinetics of the effects of the 3 treatment types: chemotherapy, hormonotherapy, or both simultaneously;

2) The dynamic relationships between PSA and CTC kinetics: these 2 variables had no clear direct relationships, but were triggered by a common unobserved variable;

3) The joint modeling of 2 dependent variables of different types: count (CTCs) and continuous data (PSA);

4) The sampling statistics of blood collection: the observed CTC count from a 7.5mL aliquot of blood ($CTC_{Aliquot}$) is a sample of a true CTC counts in the total blood volume (CTC_{Total}). For instance, CTC equal to 0 does not imply that no CTCs are produced.

In order to take into account the inter-individual variability in the kinetic profiles, the population analysis was performed with a non-linear mixed effects model using NONMEM 7.3. Selection and evaluation of the best model were achieved using criteria based on the likelihood, goodness-of-fit plots and simulation-based diagnostics.

Results:

Model structure:

The 4 levels of complexity were considered in the final model:

1) Since no drug concentration data were available, a K-PD approach has been used for the kinetics of treatment effects. Chemotherapy and hormonotherapy administrations were assigned to 2 K-PD compartments, allowing the estimation of different kinetic and efficacy parameters for chemotherapy and hormonotherapy.

2) Their respective effects on both PSA and CTCs were mediated through a latent variable, defined as an underlying, non-observed variable. Each treatment was acting as an inhibitor of the latent variable production.

3) The PSA kinetics was described by a non-steady-state 1-compartment model with 0-order production and 1st order elimination rates.

The CTC kinetics was characterized by a cell life span model, commonly used for the modeling of blood cell maturation [2]. The main assumption of the cell life span model is that each CTC has the same life span (LS), so that the rate of CTC loss at time *t+LS* is equal to the production rate at time *t*.

4) The CTCs being counted from a 7.5mL blood sample, a Poisson process for the $CTC_{Aliquot}$ was considered for the discrete sampling techniques, applying a scaling factor (α=(aliquot volume)/(total blood volume)). Different Poisson related models were tested. The best one was the negative binomial distribution, which allowed taking into account the overdispersion (variance>mean) of observed $CTC_{Aliquot}$ counts.

Model evaluation:

According to goodness-of-fit plots, PSA kinetics in treated CRPC patients were properly fit over the 6-month period, and Visual Predictive Check (VPC) showed good agreement between the distribution of observed and simulated values.

The predictive performance for the CTCs was assessed with simulation-based diagnostics: categorical VPCs, CTC count distributions and overdispersion plots (variance vs mean).

Relative Standard Errors of typical mean parameters and inter-individual variability, representative of estimation precision, were all less than 40%.

Finally, the model enabled simulations of different types of kinetics profiles, similarly to those observed.

Parameter interpretation:

Parameter estimates showed an inhibitory effect for latent variable of the chemotherapy superior to the hormonotherapy, as expected. The CTC life span was estimated at 97 days, and its production rate at 160 $CTC.day^{-1}.AU^{-1}$. The PSA half-life was assessed at 65 days, and its production rate at 2 $ng.mL^{-1}.day^{-1}.AU^{-1}$. The ratio of production rates was equal to 0.01 $ng.mL^{-1}.CTC$.

Conclusions:

The proposed semi-mechanistic K-PD model is the first to quantify the dynamic relationships between the kinetics of PSA and CTC count in metastatic CRPC patients. This is an atypical model combining several advanced features in pharmacometrics: K-PD modeling, joint modeling of count and continuous data, both driven by a latent variable and the discrete processes for CTC modeled by a cell life span model combined to random sampling statistics. The latent variable could be interpreted as the non-measured tumor burden producing CTCs and PSA.

This model allowed simulations of different kinetic profiles, and enabled to obtain information about PSA and CTC production and CTC life span and its inter-individual variability.

It will be challenged for evaluating the prognostic value of CTC count and PSA: i) to identify some covariates explaining the variability; ii) to establish a link between a CTC kinetic parameter and survival; iii) to test the sensitivity and specificity of the early modeled decrease in marker for predicting survival.

The proposed model would potentially help oncologists in the evaluation of CRPC patients' response to chemotherapy and hormonotherapy.

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Scott Marshall C-06 Good Practices in Model Informed Drug Discovery and Development (MID3): Practice, Application, Documentation and Reporting

EFPIA MID3 workgroup : Scott Marshall (5) Rolf Burghaus (1) Valerie Cosson (2) S. Y. Amy Cheung (3) Marylore Chenel (11) Oscar DellaPasqua (4) Nicolas Frey(2) Bengt Hamren (3) Lutz Harnisch (5) Frederic Ivanow (6) Thomas Kerbusch (7) Joerg Lippert (1) Pet
(1) Bayer (2) F. Hoffmann-La Roche (3) AstraZeneca (4) GlaxoSmithKline (5) Pfizer (6) Johnson & Johnson (7) Merck/MSD (8) Boehringer Ingelheim Pharma GmbH & Co. KG (9) Novartis (10) Novo Nordisk (11) Servier

Objectives: The workgroup evolved from the original 2011 EFPIA /EMA M&S workshop committee. The aim was to continue a dialogue with EMA MSWG colleagues [1], realise EFPIA's commitments and enable an era of Model Informed Drug Discovery and Development (MID3) and Model Informed Regulatory Assessment [2-6].

Methods :A focus for the working group was the development of a "Good Practice and Standards" guidance document. Its aim was to promote a wider understanding of how MID3 could be applied across R&D (Part 1) and enhance both the clarity and efficiency in the reporting of MID3 analyses for regulatory interactions (Part 2). Detailed technical content was considered out of scope.

Results: Part 1 provides the rationale behind the MID3 paradigm, from utility in knowledge integration to provision of a framework to aid extrapolation (high regulatory impact situations). This section also provides a "good practice" grid to aid identification of pertinent questions across different themes (including Risk/Benefit and commercial viability) and activity levels (related to compound, mechanism and disease) to facilitate strategic planning of MID3 activities. A high level comparison of potential modelling approaches (from Empirical to systems pharmacology) is additionally outlined. Finally, examples illustrating this framework in practice, highlighting the internal impact across different application sub-types (from Selection and Validation of Drug Targets to Commercial Strategies) are described.
Part 2 outlines good practices in the documentation for analyses, covering some guiding principles, documentation in regulatory submissions and QA\QC. Consideration is given to the key components of the analysis plan, simulation plan and report, with suggestions for an appropriate and acceptable level of documentation ("fit for purpose"). An important recommendation is for an explicit statement of the underlying Stat/Math, Physiological, Pharmacological and Disease related assumptions and their evaluation, both in the planning and reporting of analyses. Members of EMA MSWG were involved in the review of the document and are aligned with the covered principles.

Conclusions: Through increasing the consistency, quality and transparency of conduct and reporting of MID3 activities, we believe this document will be an important step in achieving a greater harmonisation of these approaches across the Pharmaceutical Industry and in its interactions with Regulatory Agencies.

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Terry Shepard C-07 How European Regulators are Facilitating the Use of Modelling and Simulation: MSWG History, Activity and Future

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Objectives: The Modelling and Simulation Working Group (MSWG) was established in January 2013 to answer EMA's commitment to increase the regulatory M&S competence in Europe by coordinating the expertise across member states to provide a consistent approach in product-related and methodology related discussions [1].

Methods: The MSWG is comprised of experts across member states with advanced knowledge of modelling and simulation methodology, hands on experience in computational techniques, such as population PK, PK/PD, PBPK (physiologically based pharmacokinetic) and complex statistical M&S. Procedures are referred to MSWG from the Scientific Advice Working Party (SAWP), the Paediatric Committee (PDCO) and the Committee for Medicinal Products for Human Use (CHMP). The MSWG provides feedback in the form of written reports during monthly meetings in parallel with SAWP plenary and discussion meetings.

Results: During 2013, a total of 59 procedures were referred by SAWP (54, including three qualification procedures), PDCO (4) and CHMP (1). Most frequent applications of modelling and simulation included dose finding, dose recommendations and extrapolation. Specific examples, including feedback on experience of documentation will be presented as well as other activities (e.g. development of guidelines) and collaborations (e.g. EFPIA).

Conclusions: The MSWG have begun to increase awareness and acceptance of modelling and simulation approaches across the European national authorities through their involvement in procedures to date. CHMP endorses M&S as a systematic quantitative approach to support well informed drug development and regulatory decisions. In the longer term, it is envisaged that integrated data analysis encompassing all stages of development, based on modelling and simulations, will be important during MAA assessment, with the objective to reduce uncertainties, inform the SmPC and optimise the risk management plan (RMP). In addition it is expected that M&S (i.e. systems models) could serve as a knowledge management platform combining data across products which could be used to assist development and regulatory decisions. The MSWG, through published annual work plans will continue to work to facilitate the CHMP vision.

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Efthymios Manolis C-08 EMA qualification of novel methodologies: are we ready for M&S ?

Efthymios Manolis
EMA

Objectives: Engage industry, academia and the European Medicines Agency in discussions on how to qualify modelling & simulation (M&S) platforms to a level of standards that could be used as an integral part of drug development and subsequently in the regulatory submissions.

Methods: Since the launch of the qualification process in 2009 (1), the CHMP reviewed/is reviewing 62 requests for qualification advice or opinion (as of Mar 2014) related to biomarkers (BM) or other novel drug development tools (e.g. patient reported outcome measures, modelling and statistical methods). The qualification opinions are available on the EMA website (2). Also there is a trend of increasing numbers of qualification requests to CHMP, indicative of the pace that targeted drug development and personalised medicine is gaining and the need to bring the new tools from research to drug development and clinical use. The focus of the presentation is the regulatory experience gained so far from the CHMP qualification procedure. The different methodologies/biomarkers submitted for qualification are mapped against the drug lifecycle.

Different M&S methods have already been discussed in different contexts of use resulting in two positive qualification opinions and more advices. Experience from recent qualifications and drug development programs submitted to the Agency point to the fact that there are additional areas where modelling and simulation could have an impact. The suitability of qualification procedure for M&S, and the readiness of the modelling platforms, sponsors and regulators to engage to a strategic partnership towards qualifications will be discussed.

Conclusions: M&S is a powerful tool but in order to reach its full potential it would be essential to initiate discussions with industry, academia and regulators on its qualification and use. The qualification procedure provides the forum for such discussions.

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Björn Bornkamp C-11 The MCP-Mod methodology - A statistical methodology for dose-response

Björn Bornkamp & Frank Bretz
Novartis

The ICH E9 guidance requires pre-specification of the data analysis technique for the analysis of the primary variable(s) in the trial protocol. For dose-response modelling this would mean that the used dose-response model would be pre-specified. This is in many situations difficult, because at the trial design stage it is not precisely known which model will be adequate. As a consequence of this model uncertainty, traditionally the assumptions made on the functional form for the dose-response relationship for the pre-specified analysis are kept at a minimum, in the extreme case leading to models that treat dose as a categorical variable (i.e. making no assumption on the dose-response relationship).

The Multiple Comparison Procedures and Modeling technique (MCP-Mod) ([1], [2]) is an alternative to such an approach. Its main idea is to deal with the resulting model uncertainty through the introduction of a candidate set of dose-response models (instead of one dose-response model) that is pre-specified at the design stage. Once the data are obtained, one then uses the whole candidate set of dose-response models to test for a dose-response signal (the MCP step) and to model the dose-response curve (the Mod step) either using model selection or model averaging techniques.

After a general tutorial overview of the MCP-Mod methodology, we will present an example data analysis, where we illustrate the usage of MCP-Mod in context of a longitudinal model. We will also provide an overview of the qualification opinion issued by the EMA in January this year [3].

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Vikram Sinha C-12 The Role of Model Based Drug Development – Is it time to repaint the canvas?

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FDA

Drug development and regulatory decisions are driven by information that is compiled primarily from clinical trials and other supportive experiments, but also through clinical experience in the post-market period. The wisdom of these decisions determines the efficiency of drug development, the decision to approve the drug, and the resultant guidance on how to use the product, in the label.

While the decisions are usually simple in nature (e.g., trial design and project progression at the company, product and labeling approval at FDA), the data informing the decision are complex and diverse. The used of models in informing decisions (MBDD) with an intent to build a mathematical model of the pertinent physiology includes a pharmacokinetic/pharmacodynamic drug model that tells us how the compound works. It is used to simulate clinical trials in which the following elements can be tested: 1) Develop and test hypotheses for optimizing dosing, 2) simulate alternative dosing strategies, 3) simulate alternative patient populations and, 3) simulate alternative combination treatments.

In addition to ensuring quality standards, regulators are looking for evidence regarding appropriate dosing, consistency among multiple end points and evidence that benefits exceed harms. Many of these elements can be ascertained before a phase 3 trial is conducted. Indeed, what constitutes confirmatory evidence in support of confirmatory trials has been a subject of much debate. Since the first days of the science of pharmacology, evidence of “dose-response” has always constituted the strongest possible positive evidence of a pharmacologic mechanism of action. As our understanding of pharmacologic and pathophysiologic mechanisms increases and more drugs are designed to interact with specific receptors whose links to pathophysiologic mechanisms are well understood, drugs whose pharmacologic mechanism of benefit remains uncertain will constitute a smaller fraction of candidates for development and approval. Thus, MBDD offer an important learning tool not only into mech anistic insights but require clear expression of assumptions and expectations. The single-most important strength of such analyses is its ability to integrate knowledge across the development program, compounds, and biology.

This presentation will address the role and scope of model based drug development throughout the drug development process with a focus on the role its role in regulatory decision making. Challenges faced regarding modeling and simulation in drug development and strategies to foster and advance appropriate use of modeling and simulation across disciplines will be discussed. Specific use of MBDD in the following areas will be discussed 1) Role of M&S for a trial/program design (e.g. pediatrics) 2) Characterization of dose (exposure) response and dose justification 3) Characterization of multiple endpoints and 4) Subgroup analysis.

Camille Vong C-14 In silico comparison of MTD determination in a phase I dose-finding framework

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Objectives: Determination of a maximum tolerated dose (MTD) still relies mainly on dose escalation studies using the algorithm-based 3+3 design although it has repeatedly been shown to be biased and to provide an imprecise MTD [1]. Alternative methods, i.e. the Continuous Reassessment Method (CRM), are increasingly gaining interest for Phase I studies. We propose here to develop an in silico CTS framework for multiple comparisons of MTD determination and to highlight the potential benefits to shift from a 3+3 design to more model-based methods.

Methods: Thrombocytopenia was used as the Dose Limiting Toxicity (DLT) in two 3+3 dose escalation trials in solid tumors (study 1) and in ovarian cancer (study 2). The "reference" recommended Phase II dose (RP2D) was assessed by simulating with the PKPD model [2,3] the dose resulting in 33% of the patients with grade 4 thrombocytopenia. A 3+3 design algorithm was implemented in R to compute the RP2D distributions. The CRM was conducted using the bcrm R package [4], assuming a non-informative prior distribution and a power function to describe the dose-toxicity relationship. Stopping rule was stated when original study sizes were included.

Results: 90 and 105 mg/m^2 were identified as the reference RP2Ds for study 1 and 2, respectively. The simulated distributions of RP2D 3+3 designs were centered at 60 and 75 mg/m^2, respectively, with 90% CIs of 30-120mg/m^2 for both studies. Less than 13% of simulated trials selected the reference RP2D, and 74% and 82% of the trials for study 1 and 2, respectively, underpredicted the true RP2D. For both studies, median RP2Ds were 90 mg/m^2 using CRM. 41% of the CRM-simulated trials correctly selected the reference RP2D and 30 and 20% selected lower and higher doses in study 1. In study 2, 37% of the trials correctly designated the reference RP2D, with 25 and 20% preferring adjacent doses.

Conclusions: A comparison of different phase I oncology designs was successfully implemented using a thrombocytopenia PKPD model. The CRM method was shown to be in agreement with the reference model-based RP2D and provided a gain of 2 higher dose levels than the RP2D recommended from the 3+3 design approach. Furthermore, CRM provided a better precision of RP2D. This work is in line with the methodology shift advocated by regulators and academics in phase I oncology studies.

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Coen van Hasselt C-15 Towards early integrated mechanism-based prediction of clinical outcome and cost-effectiveness in castration-resistant prostate cancer

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Objectives: Disease progression (DP) of prostate cancer (PC) is characterized by rising levels of prostate-specific antigen (PSA) [1]. Models linking DP with clinical outcome models (CO) have been proposed for early prediction of efficacy in oncology [2]. However, predicted efficacy will also be influenced by toxicity profiles and dose reduction strategies. Cost-effectiveness is becoming increasingly important, although such analyses are mostly only performed in late-phase development. The objective of this analysis was to develop an integrated modeling framework for castration-resistant PC (CRPC) in patients treated with eribulin, which may serve as a proof-of-concept example for prediction of clinical utility and cost-effectiveness during early clinical development.

Methods and results: Based on historical data of patients receiving eribulin we developed a dynamic K-PD DP model for PSA. Model parameters were estimated with adequate precision (relative standard error, RSE <44.6%). Subsequently, a parametric Weibull model was developed which included treatment-related (time-to-PSA nadir), disease-specific (PSA growth rate), and patient-specific (ECOG score) covariates. A semi-physiological population PK-PD model for eribulin-induced neutropenia was then implemented, which included several patient-specific covariates. Markov-transition models successfully described the time-course of toxicity grades for fatigue, anemia, diarrhea and additional AEs. Another Markov-transition model was developed to describe the ECOG time-course as a surrogate for quality of life. A >50% PSA inhibition was related to a proportional decrease of increasing ECOG-transition probabilities (0.704, RSE 36%). Finally, a log-logistic survival model best described dropout.

Subsequently, an integrated simulation framework combining the different sub-models was implemented. Different simulation scenarios were defined to evaluate the impact alternative dose regimens, disease progression criteria, dose reduction protocols and specific patient-characteristics.

Conclusion: An innovative integrated simulation framework was developed that can be applied for early assessment of clinical utility and cost-effectiveness. The framework can potentially be used to support early trial design in CRPC, but also may also serve as a proof-of-concept example that can be applied for model-based drug development in oncology.

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Edouard Ollier D-01 Group comparison with fused lasso penalized likelihood: an alternative to test based methods

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Context: Group comparaison methods for Non-linear mixed effects models (NLMEM) enable to identify parameters whose estimations significantly vary across the groups. They are classicaly based on statistical tests [1]. The main drawback of test-based methods could be their lack of sensitivity for studies with low statistical power. An alternative would be to choose the model that minimize a criteria like the Bayesian Information Criterion (BIC) [2]. The principal issue of this strategy is that the BIC of all the possible sub-models have to be evaluated. A solution is then to preselect only relevant sub-models with a penalized likelyhood method where the penalty enforces parameters to be equal across the groups. This is the case of the fused lasso penalty [3].

Objectives: Our objective was to develop a version of the SAEM algorithm that maximizes a likelihood penalized by a fused lasso penalty on both fixed effects and variance of random effects.

Methods: The fused lasso penalty was applied on fixed effects and random effect variances to the joint estimation problem's likelihood which corresponds to the sum of the likelihoods of each group. Without the penalty term, maximizing this likelihood is equivalent to estimate a NLMEM independently in each group. The penalty strength is tuned by the sparsity parameter. When it is infinite, the penalty forces all the groups to have equal parameters (models are exactly the same in each group). A grid of possible values (user defined) for the sparsity parameter was tested and the optimal one is chosen using the BIC criterion.

We implemented a modified SAEM algorithm to solve the penalized likelihood problem. It follows the principle described by Bertrand et al [4].

The performance of the proposed method has been compared to a classical test based method on simulated data sets. Finaly we applied it to the analysis of a two way cross over trial studying the drug-durg interaction in 10 healthy subjects [5].

Results/Conclusions: The SAEM algorithm for fused lasso penalized maximum likelihood problems has been succefully implemented. Optimal model selection with the BIC criterion tend to be more powerful than the standard test based method on the simulated data sets, especially in design with small number of subjects. Results on real data were coherent with previously published results. The principal drawback of this method is that the grid of sparsity parameters values as to be user defined.

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Elin Svensson D-02 Prediction of pharmacokinetic interactions for drugs with a long half-life - evidence for the need of model-based analysis

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Objectives: DDI studies are commonly performed as single-dose crossover studies where AUC and Cmax w/wo perpetrator drug are compared [1,2]. The standard method to estimate secondary PK parameters is non-compartmental analysis (NCA), and geometric mean ratios (GMR) are reported. Victim drugs with long elimination half-life cause challenges. We here summarize experiences from our work with bedaquiline (BDQ, terminal half-life ~5 months) comparing NCA and model-based analysis.

Methods: Data originated from a DDI study with efavirenz (EFV) including 2 BDQ doses and sampling of BDQ and metabolite M2 over 14 days after each [3]. NLME modelling was performed in NONMEM 7.2 with FOCE-I [4]. NCA analysis was carried out on observed and simulated (n=1000) data.
Five DDI scenarios were evaluated with simulations (n=100): BDQ and M2 CL changed with factors 0.2, 0.5, 1, 2 and 5. Model parameters were re-estimated based on simulated data. GMRs of NCA AUC0-14d w/wo interacting drug were calculated and compared to expected change in steady state exposure (Css,avg). The value of metabolite data for prediction of the interaction effect on the parent drug was evaluated by comparing parameter precision after estimation w/wo metabolite data.

Results: CL of BDQ and M2 increased to 207% (RSE 3.6%) with EFV, corresponding to a Css,avg that is 48% of that without EFV. NCA GMRs of AUC0-14d based on observed and simulated data (95% CI) predicted Css,avg to 87% (70-89%)/128% (107-134%) for BDQ/M2.
The median (IQR) of the model-based predictions of change in Css,avg of both BDQ and M2 in the simulations (5, 2, 1, 0.5 and 0.2 expected) were 4.94 (4.74-5.13), 1.98 (1.92-2.06), 0.99 (0.96-1.02), 0.50 (0.48-0.51) and 0.20 (0.19-0.21), respectively. The NCA GMRs were for BDQ 1.77 (1.69-1.84), 1.49 (1.43-1.53), 1.14 (1.10-1.18), 0.80 (0.76-0.82) and 0.41 (0.39-0.43), for M2 0.99 (0.97-1.02), 1.28 (1.24-1.32), 1.38 (1.32-1.42), 1.20 (1.15-1-25) and 0.72 (0.67-0.75). Standard error of the parameter for interaction effect on BDQ CL increased more than 5-fold without M2 data; in simulated scenarios corresponding values were on average nearly 4-fold increased.

Conclusions: NCA of data from typical DDI studies when full time-concentration profiles are not captured consistently underestimated the impact of an interaction. The bias demonstrated is large enough to misguide decision making. Model-based analysis accurately predicted expected change in Css,avg and allows use of metabolite data to improves precision.

Acknowledgement:
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Yasunori Aoki D-03 Averaged Model Based Decision Making for Dose Selection Studies

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Objective: Approximately one third of the cost of a drug development program incurs in Phase III clinical studies, hence the correctness of the dose selection decisions at the end of Phase IIb studies largely influence the overall cost of drug development.

In this work, we introduce an averaged model based methodology for selecting the minimum effective dose from Phase IIb study data. We demonstrate this methodology through simulation studies of an asthma drug, with FEV1 as a biomarker, and confirm that it accurately quantifies the risk of choosing the wrong dose hence can guide more accurate dose selection decisions than the traditional pairwise dose selection criterion.

Methodology: The key idea of this methodology is to incorporate both the model parameter estimation uncertainty and the model structure uncertainty in dose selection. We average the parameter estimation uncertainty over the multiple candidate models weighted by the Akaike Criterion to compute the likelihood of each candidate dose being the correct minimum effective dose.

We have generated 5 000 sets of simulated datasets by adding artificial dose response relationships to the FEV1 placebo data. For each simulated dataset, the model structure of the artificial dose response relationship was chosen randomly from different models and model parameters were also chosen randomly.

For each data set, we have conducted the dose selection by following the traditional study protocol, and also by using the proposed methodology. After selecting the doses for all the simulated datasets using both criterions, we have counted the number of times each criterion has chosen the correct minimum effective dose.

In addition, to increase the numerical stability of the parameter uncertainty quantification calculation, we have implemented a preconditioning technique.

Results: We have confirmed through the simulation study that the proposed averaged model based dose selection criterion chooses the correct dose consistently more often than the traditional pairwise approach in various scenarios. On average, the probability of choosing the right dose was 40% using the traditional approach while it has increased to 60% by using the proposed methodology.

Conclusion: We have constructed the model averaged based dose selection methodology and demonstrated through simulation studies that the proposed methodology has a potential to increase the accuracy of the dose selections at the end of the Phase IIb clinical studies.

Sharon Hori D-06 Modeling cancer blood biomarker dynamics in relation to tumor growth

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Objectives: Cancer biomarkers, such as proteins that are shed (secreted or released) into the bloodstream from a tumor, may be useful for detecting early-stage cancers. However, it is not clear whether cancer blood biomarker levels correlate with tumor burden, especially for early-stage (sub-centimeter) tumors [1]. The aim of this work was to apply an integrative modeling-experimental approach to investigate whether plasma levels of a cancer-specific biomarker could be used as a surrogate measure of tumor cell viability, as measured using preclinical (mouse) cancer models and *in vivo* imaging.

Methods: We engineered ovarian cancer cell lines to express both an artificial tumor-specific secreted biomarker and a bioluminescence imaging reporter and then implanted these cells into the mouse ovary. We monitored the resulting tumor growth for up to 28 days using biweekly plasma biomarker samples obtained just prior to *in vivo* bioluminescence imaging (to assess tumor viability). We extended our previous mathematical model of biomarker shedding [1] to account for biomarker present in the extravascular space and obtained estimates for individualized plasma biomarker shedding rates in relation to *in vivo* tumor growth. Model simulations and parameter estimates were obtained using Simulation and Analysis Software II (SAAM II).

Results: We showed that a model of biomarker shedding composed of two ordinary differential equations best fitted the preclinical plasma biomarker data for up to 15 days of early tumor growth in n = 18 mice. The fitted model provided a qualitatively excellent description of all individual mouse plasma biomarker kinetic data, with reasonably low standard errors on individual parameter estimates (< 25% CV). Furthermore, plasma biomarker levels correlated well with tumor cell viability as measured using bioluminescence imaging (R^2 = 0.86). Of note, the *in vivo* tumor-specific biomarker shedding rate was estimated to be 7×10^{-5} ng/day/cell. This represents the first in vivo estimate of cancer biomarker shedding rates. We further explored a range of parameter values that may be exhibited by current clinical biomarkers by performing a 1-way sensitivity analysis by simulating plasma biomarker levels while increasing/decreasing the value of a single parameter estimate up to 1000-fold.

Conclusions: We showed that during early tumor growth, tumor-specific plasma biomarker levels correlate well with tumor viability. The mathematical model developed here can be extended to virtually any solid cancer and applied to the analysis of correlations between biomarker shedding and tumor size in other *in vivo* preclinical models.

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Rik de Greef D-07 Modeling of tumor size reduction patterns in advanced melanoma under treatment with MK-3475, a potent antibody against PD-1

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Objectives: Limited information is available on the dynamics of tumor size (TS) in advanced melanoma. In the current analysis a population model was developed based on TS data from patients treated with MK-3475, a potent immune modulating antibody against PD1, to characterize the patterns of TS dynamics and to investigate the influence of covariates.

Methods: In a phase I clinical trial, 411 patients with advanced melanoma received MK-3475 at different dose levels, see also [1]. TS was quantifiable as the sum of the longest dimensions of all target lesions by RECIST 1.1 assessment in 364 patients. A mixed effects model describing TS over time was developed on the basis of the model by Claret et al. [2] in Nonmem7.1 [3]. Model performance was assessed by bootstraps and VPCs using PsN [4].

Results: TS patterns over time after dosing of MK-3475 appeared to differentiate from available literature [2, 5]; especially little to no tumor regrowth was present. The Claret model was modified to accommodate this and other features of the data. Specifically, heterogeneities in the data reduced the adequacy of standard variability components as was particularly visible in VPCs. Four patterns of tumor growth and shrinkage were discernable in the data and characterized using four mixture groups in the $MIX functionality of NONMEM. Particular adjustments were made to also include patients without post-baseline measurements. Subsequent stepwise covariate modeling identified the baseline number of target lesions, number of lymph node lesions and ECOG scores as significant and influential covariates. Baseline TS was also an important correlate of tumor response and was incorporated into the model through the mixture component. When accounting for these covariates, pretreatment with ipilimumab was not a significant predictor of tumor size change despite a higher disease burden in these patients.

Conclusions: A mixed effects model capturing tumor size reduction in melanoma patients dosed with MK-3475 was successfully developed. In a new approach, patterns in tumor size reduction under treatment with this immune modulator were characterized using mixture components. Baseline tumor size, number of target lesions and number of lymph node lesions were identified as important covariates in the response to treatment.

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Pauline Mazzocco D-08 A mixed-effect modeling framework to personalize treatment of low-grade glioma patients

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Objective: We aim to develop a mixed-effect modeling framework to predict the effect and the duration of temozolomide (TMZ) treatment in low-grade glioma (LGG) patients.

Method: We analyze a dataset containing mean tumor diameters (MTD) in 77 LGG patients treated with TMZ (952 total observations). Among these 77 patients, 45 (58%) experienced tumor progression after 14.3 months in median from treatment onset, this progression occurring during treatment for 28 patients (36%). We propose a mixed-effect model to describe the observed MTD, accounting for possible tumor progression during treatment. Model parameters are estimated with Monolix (Lixoft). Genetic statuses (1p19q codeletion and p53 mutation) are included as covariates with a stepwise forward/backward analysis [1].
We investigate the ability of the model to predict 2 clinically-relevant metrics:
1- the time to tumor growth (TTG)
2- the minimal tumor size (MTS).
We only consider observations before the 3rd month of treatment to compute the empirical Bayes estimates (EBE) of the individual parameters, using a MAP algorithm implemented in Matlab (Mathworks) and MLXTRAN. EBEs are used to simulate the model and compute the 2 metrics in the 45 patients with observed progression.

Results: With model simulations we find that beyond 18 months of treatment, p53-mutated patients have a smaller TTG (less effective treatment) compared to the others and more than 50% of them experience tumor progression during treatment. The MTS is also always worse for p53-mutated patients.
Regarding individual prediction capability, the prediction of TTG is correct until 24 months following treatment onset. Beyond that, the model tends to under-estimate the effect of TMZ. For 85% of patients (38 patients), the MTS is correctly predicted, i.e the error on the prediction is less than 20% relatively to the tumor size at treatment onset, which represents an error of less than 1cm.

Conclusions: Our results indicate that knowing whether a LGG patient is p53-mutated or not is the first step to personalize his/her therapy, 18 months of TMZ appearing to be a maximum for p53-mutated patients. Extracting information through the MAP algorithm only based on observations before the 3rd month of treatment is sufficient to predict the amplitude of the response for 85% of patients and its duration for 2 years.
As a perspective, this modeling framework can be used by clinicians to personalize the duration of TMZ treatment in LGG patients.

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Nick Holford D-09 Power and Type 1 Error of Tumour Size Metrics Used to Predict Survival

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Objectives: A quantitative disease progress model for non-small cell lung cancer growth and response to treatment was described in 2008 [1]. Subsequent reports have described a link of tumour size with survival but the link between drug exposure and response has either not been considered [2] or has not been based on plausible pharmacological mechanisms [3,4]. It is expected that mechanism based pharmacological models applied to effects on tumour growth will be more robust and better suited for prediction of suitable doses and dosing schedules.

Metrics based on tumour size to baseline ratio at 6 weeks (TSR6 [2]) or baseline plus fractional change from baseline at 8 weeks (S0FC8 [5]) and the time to tumour growth with Weibull baseline hazard (WTTG [6]) have been proposed to detect treatment effects on survival. A hazard based approach to prediction of survival would suggest that consideration of the time course of disease progress would be more likely to be informative [7].

The objectives of this study were to determine the tumour metric which had acceptable Type 1 error when there was no treatment effect on survival and which had sufficient power to detect a treatment effect on survival.

Methods: A mixed effect modelling approach using simulation has been used to examine the Type 1 error associated with using EBE derived tumour response metrics and to estimate the power of suitable metrics to detect treatment effects. 1000 trials with 100 subjects randomized to placebo or 3 active doses were simulated under the assumption that survival hazard was either not related to tumour size or was proportional to tumour size.

Results: Type 1 error rates for TSR6 (90%), WTTG (29%) and S0FC8 (12%) were greater than nominal 5% when the mean survival time was 1 year. The full time course of predicted tumour size did not have inflated Type 1 error and was the most powerful metric to detect a treatment effect on survival. It is no more complex to compute than other size based EBE metrics.

Conclusions: The full predicted time course of tumour size is recommended for detection of treatment effects on survival that are linked to changes in tumour size.

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María José García Sánchez I-09 PBPK analysis of doxorrubicin tissue uptake by Simcyp® simulator: influence of gender related variables

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Objectives: to evaluate the influence of gender related biological differences on pharmacokinetics (PK) and tissue uptake of doxorubicin (DX) using the physiological based PK model implemented in Simcyp® simulator.

Methods: literature information about physicochemical characteristics [1] and PK parameters of DX was collected in order to include this drug as a new compound of Simcyp®. Simulation of plasma and tissue profiles of DX was performed selecting the full PBPK model. Virtual assays were performed in 100 healthy volunteers fixing the gender to 100 % and 0 % females, respectively [1]. A standard intravenous dosage of 50 mg/m^2 perfused for fixed 15, 30 and 60 min was simulated and comparison of plasma and tissues profiles for both sex was performed.

Results: literature review of drug PK data reveal that information on tissue uptake and partition coefficient (R) values are very scarce, although all studies agree on DNA relevance and extremely high R values for all tissues, being kidney the one reaching the highest value [3]. Simulated profiles in plasma reveal narrow confidence intervals in the female population compared to male population due to a wider dispersion of heights values into the male population considered in Simcyp®. This fact leads to relevant differences in perfusion rates among individual showing extreme height values when drug is administered at a fixed perfusion time. Interesting differences were also found when comparing heart tissues profiles between males and females. Despite the higher cardiac output in males compared to females the total blood flow to heart tissue is lower; accordingly the simulated curves in this tissue show that the maximum concentrations reached are about 30 % higher in the female population than those reached in males.

Conclusions: results from PBPK model applied to DX using Simcyp® simulator reveals that gender related differences affect doxorubicin PK in adult population, with higher values of maximum concentrations in heart tissue predicted for woman than those predicted for men. This fact could be of clinical relevance taking in account the high cardiotoxicity of DX.

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Joomi Lee II-10 Population pharmacokinetic analysis of sumatriptan in healthy Korean male subjects

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Objectives: Sumatriptan, a selective agonist for vascular serotonin (5-HT1) receptor causing vasoconstriction of cerebral arteries is used for the acute treatment of migraine attack with or without aura. Despite its relatively high inter-individual variability, few reports have addressed the pharmacokinetic (PK) modeling of sumatriptan. The aim of this study was to develop a population PK model of sumatriptan in healthy Korean subjects.

Methods: Plasma data after a single oral dose of 50-mg of sumatriptan in 26 healthy Korean male subjects were used. Blood samples were collected at 0 (predose), 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 UPLC/MS/MS. We estimated a population PK analysis of sumatriptan using a NONMEM (Ver. 7.2).

Results: A two-compartment disposition model described the best fit to a total of 728 concentrations. Because absorption kinetics patterns showed double peak, Erlang's absorption and first-order elimination model were recruited. There were no significant covariates affecting PK parameters. The visual predictive check indicated that the PK profile of sumatriptan was adequately described by the proposed population PK model.

Conclusions: A population PK model was developed and reasonable parameters were obtained from the data of healthy Korean male subjects.

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Gaohua Lu II-16 Developing a mechanistic physiologically based lung model and its application in modelling rifampicin pharmacokinetics in the lung

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Objectives: The aim of this collaborative project between the Critical Path to TB Drug Regimens (CPTR) Consortium and Simcyp was to develop a mechanistic multi-compartment PBPK model that can be used to predict the time course of distribution of drugs into different regions of the lung after systemic administration.

Methods: To achieve this, the model should take into account drug movement across the alveolar capillary barrier (ACB) to be characterised by both passive permeability and active transport mechanisms and also to allow the physiological changes that occur following tuberculosis (TB) infection to be accounted for. The model includes various segments for airway and lobes, and each of the segments consists of 4 compartments representing the pulmonary capillary blood, pulmonary tissue mass, epithelial lining fluid and alveolar air. It accounts for pulmonary enzyme metabolism and incorporates transporter functionality at the basal and apical membrane of ACB. Major efforts were made to collate and meta-analyse data for lung physiological and anatomical parameters and any information on transporter abundance in the ACB from literature.

Results: The multiple-compartment lung model consists of 28 ordinary differential equations and c.a. 200 parameters implemented in Matlab Simulink®. Rifampicin, as a model compound, was selected and prior physicochemical and *in vitro* data along with passive permeability data from Cultured Human Airway Epithelial Cells (Calu-3) monolayer were used in the model building [1]. The predicted concentrations of pulmonary capillary blood, tissue mass and alveolar fluid after oral dose were comparable to the concentration of the systemic blood, epithelial lining fluid and alveolar cells observed clinically in adult subjects without TB [2]. TB-induced physiological parameter changes in the lung can impact the drug concentration-time profiles in different parts of the lungs and the model can effectively be used to investigate such changes and their impact on the drug response.

Conclusions: The developed lung model can provide a useful framework for investigation of new anti-TB drug's pharmacokinetics and provides insight into the impact of different drug and system parameters on the drug disposition in different lobes of the lung. Moreover as the lung model can directly connect the dosing regimen of anti-TB drugs to the expected concentration at the site of action, it paves the way for better understanding of the potential drug actions in the human pulmonary system.

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Daniel Moj II-29 Physiologically-based Pharmacokinetic (PBPK) modeling of the time-dependent drug-drug interaction (DDI) of clarithromycin and midazolam

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Objectives: Development of a descriptive and predictive time-dependent PBPK DDI model for clarithromycin (CYP3A4 substrate/inhibitor) and midazolam (CYP3A4 substrate).

Methods: PBPK models were independently developed for clarithromycin and midazolam using physicochemical properties (e.g. pka, logP) and study demographics (age, height, mass and BMI) of various clinical studies in humans. Time dependency was incorporated applying a dynamic CYP3A4 turnover model (intestinal mucosa and liver) using in vitro/vivo data (e.g. k_{deg}). Parameter identification (e.g. fraction unbound) was performed using plasma concentration-time profiles after intravenous (i.v.) infusion (clarithromycin), i.v. bolus injection (midazolam), single (clarithromycin, midazolam) and multiple oral dosing (clarithromycin). Single PBPK models were linked for DDI simulations using oral clarithromycin and oral or i.v. midazolam. Model evaluation was accomplished predicting external concentration-time profiles of the individual compounds and the DDI. Modeling was performed using PBPK-Software PK-Sim® 5.2.2 and Mobi® 3.2.2.

Results: A time-dependent PBPK DDI model for clarithromycin and midazolam was developed. A CYP3A4 turnover model was applied dynamically accounting for clarithromycin dependent irreversible CYP3A4 (auto-) inhibition. Biotransformation of midazolam was dynamically linked to organ specific CYP3A4 concentrations. An adjustment to the distribution of clarithromycin into the red blood cells compartment was required to account for accumulation in macrophages and leukocytes. Organic anion-transporting polypeptide processes of clarithromycin were incorporated. Renal clearances were estimated using urinary excretion data. Using final model parameter values the DDI model was able to describe and predict the increase in midazolam exposure due to increased degradation of CYP3A4 via clarithromycin.

Conclusion: A whole body PBPK DDI model of clarithromycin and midazolam was successfully developed using clarithromycin-dependent inhibition of CYP3A4 in a time-dependent manner. The model allows predictions of plasma concentration-time profiles of clinically relevant midazolam doses after clarithromycin administration. The presented model may serve as a valuable future tool to describe and predict time-dependent drug-drug-interactions.

Helen Musther II-31 Are PBPK models reporting the right Cmax? Central venous versus peripheral site

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Objectives: PBPK models often report over-predicted maximum concentration (Cmax) for intravenous (IV) administration compared to observed *in vivo* sampled data. It is suggested that this discrepancy may be due to PBPK models reporting the concentration in the central venous compartment, rather than the concentration at the sampling site. The objective of this project was to develop a corrective model describing a "peripheral site" concentration-time profile.

Methods: A peripheral site model was developed assuming that the surrounding tissues around the sampling site contribute, to different degrees, to its concentration. The model utilised the tissue-specific concentration-time profiles output by the full-PBPK model in the Simcyp population-based simulator (V13), and tissue "flow" fractions as defined by Levitt (2004) [1]. Tissues used in defining the peripheral site were Skin, Adipose, Muscle and a "Shunt" to describe arterio-venous anastomoses, and the flow fractions were varied based on assumptions made about the arterial contribution to the "Shunt". The model was applied to 7 different compounds where a Simcyp compound file and *in vivo* literature data following IV dosing were available. Predicted Cmax concentrations using the peripheral site model were compared to the observed Cmax at the same time point, and the difference in prediction accuracy compared to that of the central venous compartment concentration ("venous sampling") was assessed.

Results: Application of the peripheral model improved predictions of the observed Cmax value compared to the "venous sampling" in Simcyp, in particular for early time points following IV dosing. All studies investigated showed a Cmax prediction within 2-fold of the observed value when using the peripheral site model. Changing the fractional contribution of the tissues resulted in an improvement for some compounds bringing them within a 0.8-1.25-fold range, while some compounds moved outside the 2-fold range, suggesting that the original fraction was preferable in the model selected.

Conclusions: The developed peripheral site model significantly improved predictions of Cmax after IV dosing for the compounds tested. The results suggest this model should be used when comparing the predicted and observed Cmax values from PBPK models.

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Kayode Ogungbenro II-38 A physiologically based pharmacokinetic model for 6-mercaptopurine in adults and children

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Objectives: To develop a PBPK model for 6-MP in childhood acute lymphoblastic leukaemia (ALL). 6-mercaptopurine is a purine antimetabolite and prodrug that undergoes extensive intracellular metabolism to produce thionucleotides, active metabolites which have cytotoxic and immunosuppressive properties [1]. Combination therapies involving 6-mercaptopurine and methotrexate have shown remarkable results in the cure of childhood ALL in the last 30 years [2]. 6-mercaptopurine undergoes very extensive intestinal and hepatic metabolism following dosing due to the activity of xanthine oxidase leading to very low and highly variable bioavailability [3]. Despite the success recorded in its use there is still lack of effect and presence of life threatening toxicity in some patients due to variability in the pharmacokinetics. Also, dose adjustment during treatment is still based on toxicity [4].

Methods: A physiologically based pharmacokinetic model with separate compartments for plasma, red blood cells, liver, gut tissue, enterocyte, stomach, gut lumen, kidney, skin, bone marrow, spleen, thymus muscle and rest of body was developed. System parameters such as blood flows and organ volumes were obtained from the literature, some drug parameters were obtained from the literature and the rest were optimised from studies reporting plasma and intracellular red blood cell concentrations of 6-merpatopurine and its metabolites. Age-dependent changes in parameters were implemented for scaling and variability was also introduced on the parameters for prediction. The effect of genetic polymorphism in thiopurine methyltransferase was also investigated.

Results: The model adequately predicts plasma concentration after intravenous and oral doses in adults and children. The model also provides encouraging results in terms of the prediction of the concentration of 6-mercaptopurine and its metabolites in plasma and red blood cells (RBC) in the different polymorphic groups. For a standard oral dose of 75mg/m2, the concentration of 6-thioguanine nucleotide in RBC is about 30 and 2 times higher for the no activity and intermediate activity groups compared to the high activity groups respectively.

Conclusions: A physiologically based pharmacokinetic model that can predict concentrations in different tissues has been developed and this can be used for dose optimisation. This model could help to improve clinical outcome in the use of 6-mercaptopurine through better dosing.

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Jens Borghardt III-20 The physiological interpretation of population pharmacokinetic modelling results for inhaled olodaterol

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Objectives: A previously developed population pharmacokinetic model identified a three compartment systemic disposition model with a lung dose absorbed by three parallel absorption processes for inhaled olodaterol (1). After inhalation with the Respimat®, more drug deposition in higher airway generations (small airways and alveoli), where drug absorption is assumed to be fast, and less central airway deposition, where drug absorption is assumed to be slow, has been discussed (2). However, the model identified most of the lung dose to be slowly absorbed (ca. 70%, $t_{1/2}$: 48.1 h). Lysosomal trapping of olodaterol in lung cells was proposed as a plausible physiological explanation. However, lysosomal trapping is a systemic effect and, hence, should also be present after IV administration. The objective of this analysis was to investigate the hypothesis of lysosomal trapping after IV administration and inhalation of olodaterol.

Methods: Olodaterol data after IV dosing (n=48) and inhalation (n=84) was available from different trials in healthy volunteers and evaluated using a population PK approach. In contrast to the previous approach (1), urine data collected over 96 h after IV administration was included for possibly identifying an additional process that could be associated with lysosomal trapping. Analyses were performed in NONMEM 7.2 and R 2.14.2.

Results: A four compartment disposition model was identified by the re-analysis of the IV data. By including the urine data, a longer terminal half-life with 82.4 h compared with 14.0 h described by the previous IV model (without urine data) was identified, even though full plasma concentration-time profiles up to 24 hours were available in the previous analysis. Simulations indicated that the additionally identified process was masked due to the lower limit of quantification. Applying the new parameter estimates to the inhalation data did not impact the structure of the inhalation PK model. However, the slowest absorption process ($t_{1/2}$: 27.4 h) was faster compared with that of the previous inhalation model ($t_{1/2}$: 48.1 h). Consequently, flip-flop kinetics that was demonstrated for the previous model was not present in the updated model.

Conclusions: The obtained results support the hypothesis of lysosomal trapping of olodaterol after both IV administration and inhalation. Nevertheless, the large, slowly absorbed fraction of the lung dose (ca. 75%) indicates lysosomal trapping to a larger extent after inhalation of olodaterol.

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Margreke Brill III-25 Midazolam pharmacokinetics following semi-simultaneous oral and intravenous administration in morbidly obese patients before and 1 year after bariatric surgery

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Objectives: Gastric bypass/sleeve surgery is considered the most successful treatment for morbid obesity (body mass index, BMI >40 kg/m^2). As both surgery induced weight loss and gastro-intestinal alterations may influence a drugs pharmacokinetics, we aimed to quantify the influence of bariatric surgery on oral and intravenous pharmacokinetics of CYP3A substrate midazolam in patients before and 1 year post bariatric surgery.

Methods: Twenty morbidly obese patients [144.4 kg (112-186 kg)] participated before gastric bypass/sleeve surgery and 18 patients [-44.5 kg (21-58 kg)] returned 52 ± 2 weeks after surgery. On both occasions, patients received 7.5 mg oral and 5 mg i.v. midazolam separated by 160 ± 50 minutes and 21-23 blood samples were collected until 9-11 h post oral dose. Population pharmacokinetic modeling was performed using NONMEM 7.2.

Results: Midazolam concentrations of both groups were best described by a three-compartment model with equalized peripheral volumes and a transit compartment model for absorption with transit rates set equal to the absorption rate. Post bariatric surgery, population mean (RSE%) midazolam absorption rate and clearance were higher compared to before bariatric surgery [0.40 (11%) vs. 0.17 (10%) min^{-1} ($p<0.01$) and 0.68 (5%) vs. 0.49 (11%) L/min ($p<0.01$), respectively] and peripheral volume of distribution was lower [51 (11%) vs. 84 (13%) L ($p<0.01$)]. Bioavailability and central volume of distribution were similar to before surgery [0.54 (8%) and 51(14%) L, respectively].

Conclusions: Oral and i.v. midazolam pharmacokinetics in post gastric bypass/sleeve patients revealed higher oral absorption rate and clearance compared to before bariatric surgery, while the peripheral volume of distribution was lower and bioavailability was unaltered.

Eirini Christodoulou III-39 Pharmacokinetics of silibinin in mice tissues and serum after peros and intravenous administration as a HP-ß-CD lyophilized product

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Objectives: To characterize tissue[1] pharmacokinetics (PK) of the water insoluble hepatoprotective flavonoid silibinin (SLB), after *peros* and intravenous (i.v.) administration as a water soluble lyophilized product with hydroxypropyl-beta-cyclodextrin (HP-β-CD) to mice and develop open loop PBPK tissue models.

Methods: A lyophilized SLB-HP-β-CD product was administered orally (50mg/kg) and i.v. (20mg/kg) to 60 C57bl/6J male mice after reconstitution with water for injection. Mice were divided into groups of five and were sacrificed at selected time points for blood and tissue (liver, brain, kidneys, heart, lungs and spleen) sampling. Serum and homogenized tissue samples were analyzed with an HPLC method developed for SLB. Parent SLB (non-metabolized) and total SLB (metabolized plus non-metabolized, calculated after sample incubation with the enzyme β-glucuronidase) were determined. Empirical PK models were fitted to the i.v. serum data for parent SLB. The model describing the serum concentration was used as forcing function for open loop PBPK[2,3] tissue models. Perfusion and permeability limited tissue models were assessed and model selection was based on basic goodness of fit plots and the Akaike criterion. *Peros* serum data were analyzed in a similar manner, using NONMEM.

Results: SLB is rapidly and extensively absorbed from GI tract after *peros* administration of the lyophilized SLB-HP-β-CD product and highly distributed in liver, kidneys, heart and lungs after both *peros* and i.v. administration accomplishing relatively high levels in tissue homogenates. No SLB levels were detected in brain tissues, and spleen was unable to be homogenized and furthermore analyzed. Serum data were described by a bicompartmental model, parametrized as CL (3.34 ml/h/gr), V1 (1.37 ml/gr), Q (2.47 ml/h/gr) and V2 (44.3 ml/gr). Perfusion limited PBPK tissue models were used for heart, kidneys and liver and the estimated Kp values were 0.35, 2.62 and 4.31, respectively. Data from the lungs could not be analyzed. Similar results were obtained from the *peros* data. The absolute oral bioavailability of parent and total SLB after administration as a lyophilized SLB-HP-β-CD product was 20% and 45.5%, respectively.

Conclusions: Rapid and extensive absorption of SLB after *peros* administration of the lyophilized silibinin-HP-β-CD product and extensive distribution to liver, kidneys, heart and lungs is observed. The developed PBPK model can adequately predict the concentration in liver, the main target of SLB.

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Jan-Frederik Schlender IV-06 Development of a whole-body PBPK approach to assess the pharmacokinetics of xenobiotics in elderly individuals

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Objectives: Physiologically-based pharmacokinetic (PBPK) models have been widely used to assess drug kinetics in special populations. Although the need of PBPK models for healthy and frailed elderly populations has been stressed out several times, a knowledge-driven model has not been developed yet [1,2]. The aim of this study was to develop a whole-body PBPK approach to understand xenobiotic exposure in healthy aged Caucasian (65-100 years).

Methods: Anthropometric and physiological parameters related to ageing, and essentials for the prediction of drug disposition were gained from peer-reviewed literature. Age dependences for organ weights, blood flows, cardiac output, glomerular filtration rate, protein levels, enzyme activities, and tissue composition were validated and summarized in a database. A lifespan whole-body PBPK model was then developed and incorporated into the PK-Sim® database (Bayer Technology Services GmbH, Leverkusen, Germany). The model was subsequently scaled up to different ages and compared to literature values to verify the model over the human lifespan.

Results: 88 publications resulting in 724 data records for healthy elderly Caucasian individuals were gathered and processed to the database. The developed PBPK approach was verified and successfully described the age-related changes in physiological parameters.

Conclusions: This study validated the usage of a knowledge-driven PBPK lifespan model. With this developed model, anatomical and (patho-)physiological age-dependences can be predicted throughout the entire age-range. Ultimately, this model could be applied as a valuable tool to optimize the drug use, and would increase the efficiency of geriatric clinical trials, minimizing possible side effects due to drug-drug interactions.

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Thierry Wendling IV-46 Nonlinear mixed-effects modelling of the oral absorption of mavoglurant following administration of an immediate- and a modified-release formulation in healthy subjects

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Objectives: To develop a nonlinear mixed-effects model to characterise the absorption rate of mavoglurant following a single oral administration of an immediate-release (IR) and a modified-release (MR) formulation in healthy subjects under fasted and fed conditions, and to predict concentration-time profiles after twice-daily multiple doses..

Methods: Data were available from a clinical study designed to compare the pharmacokinetics of the MR and the IR forms. 43 healthy Caucasian male subjects received three doses of mavoglurant as a crossover: 50 mg in IR capsules under fasted conditions (IR-fasted), and 100 mg in a MR tablet under fasted (MR-fasted) and fed conditions (MR-fed). PK data from a study conducted to assess the effect of single intravenous (IV) doses of mavoglurant on QTc intervals in 120 healthy subjects were pooled to the oral data and analysed using NONMEM 7.2.0 [1]. Drug absorption was modelled sequentially for each oral treatment using a weighted sum of *n* inverse Gaussian (IG) density functions as an input function [2]. The input model was used to predict the typical time course of the absorption rate and of the fraction absorbed after a single administration of each treatment. NONMEM was used to simulate 1000 individual PK profiles after repeated administration of each treatment. Dose superposition was performed using *n* user-supplied functions defined in a FORTRAN subroutine [3].

Results: Mavoglurant pharmacokinetics was best described by a two-compartment model with linear elimination. While an input function equal to a sum of two IG functions was sufficiently flexible to provide a reasonable fitting to IR-fasted and MR-fed data, a sum of three IG functions best captured the multiple-peak phenomenon observed in MR-fasted data. Simulations suggest that at equal doses, a twice-daily repeated administration of the IR capsule and of the MR tablet provides a similar concentration range with lower peaks for the MR formulation, whereas concomitant administration of the MR tablet with a high fat meal leads to a higher and wider concentration range in comparison with the fasted state.

Conclusions: Modelling and simulation of mavoglurant pharmacokinetics indicate that a prolonged release of the drug in the gastrointestinal tract allows a reduction of peak plasma concentrations without substantial change in the systemic exposure provided by a prompt release. However, fatty food is likely to alter drug absorption and thus its pharmacokinetics.

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Stefan Zeiser IV-53 Whole-Body PBPK Modeling of Tacrolimus in Healthy Volunteers

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Objectives: To describe disposition of Tacrolimus (TAC) in healthy volunteers by a whole-body PBPK model based on literature data. Furthermore, to determine blood:plasma partitioning in terms of logP and fu by using plasma and whole blood concentrations simulateneously, and to estimate the fraction of hepatic clearance and intestinal first pass effect.

Methods: Physico-chemical and PK parameters of patients and healthy volunteers were gathered in a literature review. Whole blood and plasma concentrations after IV and PO administration were taken from three studies in literature [1], [2], [3]. The model was implemented in the PBPK platform PK-Sim® [4]. Elimination of TAC was described by hepatic and intestinal CYP3A4/5 together with intestinal efflux pump Pgp. The major driver of blood partitioning, FKBP12 in erythrocytes [5], [6], was implemented by a protein binding partner. Physico-chemical and PK parameters were optimized with data from [1] using a simulated annealing algorithm implemented in PK-Sim®. Estimates of logP, fu, CLint of CYP3A4/5 and binding parameters for FKBP12 are based on plasma and whole blood IV concentrations. Estimates of intestinal concentration of CYP3A4/5 and kinetic parameters of Pgp are based on plasma and whole blood PO data.

Results: Whole blood and plasma mean concentrations from [1] could simultaneously be described well. Predictions of mean plasma and whole blood concentrations were within a two-fold range of observed concentrations of European and Asian healthy volunteers from two independent studies, [2], [3]. Results from patient studies could not be reproduced without any adaptations, [7], [8]. Based on data from Möller et al., logP and fu values were determined equal to 5.82 and 0.0129, respectively. Bioavailability F with and without intestinal first pass effect were calculated to 30% and 61%, respectively.

Conclusions: TAC plasma and whole blood concentrations from [1] could simultaneously be described well. Despite the reported high variability of PK parameters whole blood concentrations in white Americans and Asian population could be predicted in an acceptable manner in a dose range from 2–5 mg. Prediction of patient data from [7] needs further investigation. Using whole blood and plasma concentrations simultaneously the estimated value of logP was at the high end of reported range, [9], [10]. Based on model prediction, intestinal first pass effect reduces bioavailability by 50% compared to hepatic clearance alone.

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Jianping Zhang IV-54 Pharmacokinetics of eltrombopag in patients with hepatic impairment

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Objectives: Eltrombopag is a non-peptide thrombopoietin receptor agonist approved for the treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based antiviral therapy. It has been reported previously that eltrombopag exposure was influenced by the severity of liver disease [1]. The objective of the present analysis was to evaluate the impact of hepatic impairment on eltrombopag pharmacokinetics (PK) in thrombocytopenic patients with hepatic impairment using population PK modelling approach.

Methods: The population PK analysis involved 742 subjects from 6 studies, of which 28 were healthy subjects, 673 were patients with HCV, and 41 were patients with liver disease of other etiology. Of the 714 patients, 642 (90%) had mild hepatic impairment (Child-Pugh Score [CPS] 5-6), 67 (9%) had moderate hepatic impairment (CPS 7-9), and 2 (9). Nonlinear mixed effects modelling was conducted using NONMEM VII. Influential covariates were evaluated using a semi-full model approach followed by backward elimination. Visual predictive check was implemented for final model evaluation.

Results: Consistent with what was reported previously [2], the eltrombopag PK was described by a linear two-compartment model with absorption lag time and dual sequential first-order absorption. Race (East+South East Asian vs. Others), gender, and severity of hepatic impairment were the primary predictors of eltrombopag CL/F, whereas Race (Central+South Asian vs. Others) and body weight were the predictors of eltrombopag Vc/F. Reduction of eltrombopag CL/F was found to be associated with the increased severity of hepatic impairment. CL/F in patients with CPS 5 was 49% lower than healthy subjects. CL/F in patients with CPS 6 was 64% lower than healthy subjects. As the severity of hepatic impairment further increased, less reduction in eltrombopag CL/F was found. For patients with CPS $\geq$8, CL/F was 69% lower than healthy subjects.

Conclusions: Population PK modelling of eltrombopag from multiple studies enabled robust quantification of the influence of hepatic impairment on eltrombopag pharmacokinetics, which further supported the eltrombopag dosing strategy in patients with greater degree of hepatic impairment.

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Yumi Emoto-Yamamoto I-03 Toward a generic PBPK model to predict drug distribution in human brain

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Background: Prediction of drug distribution in human brain is of importance for CNS drug development, but also for non-CNS drug development. Previously, PBPK rat brain distribution models have been developed separately for acetaminophen (APAP) [1], quinidine (QUIN) [2] and methotrexate (MTX) [3]. For APAP, human lumbar cerebrospinal fluid (CSF) concentrations were successfully predicted by the PBPK model, indicating the validity of this approach.

Objectives: The purpose of this research is to further develop a *generic* brain distribution PBPK model enabling the prediction of brain distribution of a drug on the basis of its physico-chemical properties.

Methods: Multilevel brain and plasma rat data on APAP, QUIN and MTX that have been used to develop the separate PBPK models was analyzed simultaneously with NONMEM, to explicitly distinguish between physico-chemical properties and systems physiological characteristics. First, drug brain distribution based on passive processes is addressed (i.e. passive permeability of the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB), brain extracellular fluid (ECF) bulk flow and CSF turnover). To that end, the “passive only” data were used (obtained following co-administration of transporter inhibitors).

Results: The passive transport clearance from plasma to brain ECF, CSF in the lateral ventricle (LV) and CSF in the cisterna magna (CM) is 27, 3.6 and 0.96 µl/min for APAP, 50, 9.0 and 1.1 µl/min for QUIN, 1.9, 0.13 and 0.018 µl/min for MTX. The passive transport clearance from brain ECF, CSF in LV and CSF in CM to plasma is 35, 5.2 and 6.1 µl/min for APAP, 6.3, 0.04 and 4.1 µl/min for QUIN, 17, 5.2 and 4.4 µl/min for MTX. The rank order of the passive transport clearance into the brain of the compounds is in line with rank order of lipophilicities at physiological pH, but not for the passive transport clearance out of the brain.

Conclusions: The currently published PBPK model for the brain drug distribution needs to be refined to a generic PBPK model by further investigation such as pH dependent passive permeability.

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Abhishek Gulati I-25 Modeling the effect of interferon beta-1b on contrast enhancing lesions in relapsing-remitting multiple sclerosis

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Background: Multiple sclerosis (MS) is a chronic autoimmune disease that may affect both white matter and gray matter [1-3]. The acute focal inflammatory events in the white matter are evident on magnetic resonance imaging (MRI) as contrast enhancing lesions (CELs). A negative binomial distribution model was recently used to best describe the CEL generation and resolution in the absence of treatment [4]. Interferon beta-1b (IFN-beta-1b) is widely used for the treatment of relapsing-remitting (RR) MS. Despite being first-line treatment, IFN-beta-1b is considered only partially effective in reducing CEL activity [2].

Objectives: The aims of this work are (1) to characterize the effect of IFN-beta-1b in preventing CEL formation and (2) to investigate its ability in promoting CEL resolution.

Methods: Nine patients with RRMS, not receiving any immunomodulatory treatment but steroids to treat clinical exacerbations, underwent monthly MRIs for 48 months [5]. The number of CELs was monthly recorded. Monthly CELs were also available from 6-months pre-therapy and 36-months therapy phases from another group of 15 RRMS patients [6]. Therapy consisted of subcutaneous administration of 250 µg IFN-beta-1b every other day for 36 months as well as steroids to treat clinical exacerbations. Using the previously published negative binomial distribution model [4] as the baseline model, effect of IFN-beta-1b was evaluated on all the model parameters using different time functions. The analyses were performed using NONMEM version 7.2 [7].

Results: IFN-beta-1b produced an expected decrease in the predicted numbers of CELs (λ) by λ_0 inhibition. No effect was identified on the Markovian elements that also define λ. The findings imply that the IFN-beta-1b might prevent the formation of new CELs but does not affect their resolution.

Conclusions: A previous study by our group [4] indicated that the use of steroids contributes to the resolution of existing CELs, but does not reduce the development of new CELs. Interestingly, the analyses performed in this study complement these findings, indicating that the use of IFN-beta-1b reduces the formation of new CELs but does not promote disappearance of already-formed CELs. These results suggest that the design of optimal therapies combining IFN-beta-1b and steroids might affect the occurrence and resolution of inflammation more effectively.

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Xiao Hu I-35 Exposure-Response Analysis of Peginterferon beta-1a in Subjects with Relapsing Remitting Multiple Sclerosis

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Objectives: To establish a population pharmacokinetic (PK) model of peginterferon beta-1a (PEGIFN) in relapsing remitting multiple sclerosis (RRMS) patients and establish the relationship between PEGIFN exposure and annualized relapse rate (ARR).

Methods: PK and ARR data were obtained from a double-blind placebo-controlled Phase 3 study in RRMS patients (n=1512), in which 125 µg subcutaneous PEGIFN every 2 (Q2W) or 4 (Q4W) weeks reduced ARR (primary endpoint) significantly, compared with placebo treatment. PEGIFN serum concentrations were fitted to a PK model using non-linear mixed-effects modelling implemented in NONMEM V7.2.0 [1]. BIIB017 exposure was represented by monthly cumulative AUC for each subject, which was derived from individual post hoc PK parameters. The relationship between cumulative AUC and mean ARR was described by a log-linear model, assuming Poisson-gamma mixture model (negative binomial model) for ARR. Parameters were estimated using Bayesian analysis with Gibbs sampling in WinBUGS v1.4.3 [2]. Non-informative priors were used for parameter estimates.

Results: The PK of PEGIFN was described by a one-compartment model with first-order absorption rate. BMI was identified as a significant covariate in the final PK model ($p<0.001$). Derived from the population PK analysis, cumulative median AUC of the Q2W group (76.8 ng/mL*hr) was approximately two times cumulative median AUC of the Q4W group (39.2 ng/mL*hr). The relationship between monthly cumulative AUC and ARR was well described by the log-linear model. In general, the ARR decreased as cumulative AUC increased. The slope for ARR reduction was steep in the Q4W AUC range, especially at below median AUC. In contrast, the slope started to level off in the Q2W AUC range. Based on model extrapolation, a higher AUC than that of the Q2W group might achieve a greater reduction in ARR. Although the model showed that Q2W dosing may not have achieved maximal ARR reduction, it demonstrated that the better efficacy of the Q2W dosing regimen as compared with the Q4W dosing regimen was driven by its greater PEGIFN exposure.

Conclusions: The model suggested that greater PEGIFN exposure in the Q2W group explain the enhanced efficacy, as accounted by ARR, observed for the Q2W group, as compared to the Q4W group.

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Kimberley Jackson I-36 Population Pharmacokinetic (PK) Modelling of Ketamine and Norketamine in Plasma, Prefrontal Cortex (PFC) and Cerebrospinal Fluid (CSF) after Subcutaneous (SC) Administration of S(+)-Ketamine in Rats.

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Objectives: The goal of the current analysis is to develop a semi-physiologically based PK model for S(+)-Ketamine (S-Ket) in rats that can be used in the future to develop PK-PD models and to translate pharmacological effects to humans.

Methods: Twenty-two Sprague-Dawley (SD) rats dosed with S-Ket were included in the study. A MetaQuant slow flow microdialysis probe was implanted in the PFC, a CSF probe in the aquaduct, and a catheter placed in the jugular vein. S-Ket was administered SC at doses of 10 mg/kg (n=10) and 25 mg/kg (n=12). Concentrations of Ket and norketamine (Nket) were measured in plasma, CSF and dialysate using HPLC and tandem mass spectrometry (MS/MS) detection. Samples were obtained at the following times (h) post dose: 0.25, 0.5, 1, 2, 3, and 4 (plasma), 0.25, 1.25, 2.25 and 4.25 (CSF). After 2 h prestabilisation, microdialysis samples (40 ml) were collected over 30 minute periods for 4 h.

The population approach in NONMEM 7.2 (Icon Development Solutions, Hanover, Maryland) was used for this analysis. The plasma PK of Ket and Nket were described using compartmental models. For concentrations in dialysate and CSF, semi-physiologically based models were evaluated where input and output rates were defined as the product of the flow and $C_P x f_u$ or C_{Tu}/KP, respectively; where C_P=predicted total analyte concentration in plasma, f_u, = unbound fraction in plasma obtained from literature, C_{Tu}=unbound concentration in CSF or dialysate, and KP=partition coefficient between unbound concentrations in plasma and tissue at equilibrium. Tissue volumes were taken from literature.

Results: Absorption after SC injection was described by a first order rate model. Bioavailability was 28% lower for the 25 mg/kg S(+)-Ket dose compared with the 10 mg/kg dose. Plasma profiles of Ket and Nket were described with compartmental models. The fraction of total plasma clearance of Ket corresponding to Nket formation was 93%. Disposition of Ket and NKet in dialysate and CSF were described adequately with the use of partial physiologically-based PK models with estimates of the partition coefficient for both analytes close to one.

Conclusions: An integrated PK model for Ket and Nket has been developed to describe disposition in plasma, dialysate, and CSF in rats following SC administration of S(+)-Ketamine. This model framework will be used to develop PK-PD models, and given the semi-physiological basis of the model, translation to other species will be attempted.

References:

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Marija Jovanovic I-43 Effect of Valproic Acid Daily Dose on Phenobarbital Clearance - Nonlinear Mixed Effects Modelling Approach

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Objectives: The aim of the study was to explore impact of valproic acid (VPA) daily dose on phenobarbital (PB) oral clearance (CL/F) in adult patients with epilepsy.

Methods: Data were collected from 136 adult epileptic patients during routine therapeutic drug monitoring. Patients administered PB either as monotherapy or in combination with other antiepileptic drugs. Daily doses of PB were in range from 25 - 300 mg and dosage regimens were once, twice or three times a day. Patients co-treated with VPA administered doses in range from 450 - 2000 mg. Nonlinear mixed effects modelling was performed for the pharmacokinetic (PK) analysis using NONMEM® software (version 7.2). A one-compartment model with first-order absorption and elimination was used as a structural model. The FOCEI was used for parameter estimation. Based on literature data volume of distribution and absorption rate constants were fixed at 0.6 l/kg and 3 h^{-1}, respectively [1]. Evaluation of final model was performed by internal validation technique.

Results: An average daily dose of PB was 130.2 ± 58.37 mg, while 25% of patients were treated with VPA dose of 1109 ± 433.9 mg/day. The interindividual variability was evaluated by an exponential model while residual variability was best described by proportional model. The estimate of CL/F for a typical patient was 0.291 l/h in the final model. PB CL/F was significantly influenced by VPA daily dose and correlation was best described by linear model. Concomitant treatment with usual VPA dose of 1000 mg/day resulted in PB CL/F average decrease of 20%. The stability of the model was confirmed by bootstrap resampling technique. The predictive performance was evaluated by adequate plots and indicated acceptable precision.

Conclusions: The final population PK model describes and quantifies influence of VPA daily dose on PB elimination. The results can be used for estimation of PB CL/F and individualization of PB dosing regimen, especially useful for patients co-treated with VPA.

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Rasmus Juul I-44 How Repeated Time To Event (RTTE) modelling of opioid requests after surgery may improve future post-operative pain management

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Objectives: Amount of opioid (eg. morphine) required by patients after surgery is often used as a surrogate measure for pain intensity in post-operative pain. However, the dynamic development of pain intensity over time is often ignored when investigating new analgesic treatments for post-operative pain[1]. This work included a Repeated Time to Event (RTTE) modelling[2] approach of repeated opioid request in order to increase the understanding of pain breakthrough patterns in severe surgeries and improve patients' pain management.

Methods: 68 patients (F:45,M:23, Age:76±15) were included from a population receiving surgery after hip fracture at Orthopaedic Department, Aalborg University Hospital, Denmark during the period May-Dec 2012. Morphine administration times (estimated precision: ±5mins), formulations and doses were extracted from medical journals in the hospitalization period or until 96 hours after surgery. RTTE modelling was performed in NONMEM 7.2 with Pirana, PsN and Xpose- and ggplot2 libraries for R[3,4]. Weibull and Gompertz distributions were investigated as hazard models. Visual Predictive Check (VPC) of Kaplan Meier survival curves as well objective function value was used to evaluate the model fit.

Results: A base RTTE model based on a Weibull distribution fitted the pooled data. However, VPCs showed that morphine request was not adequately described by the base models on all surgery types. This suggests that pain events do not occur in similar patterns in different surgeries. The developed RTTE model provide a base for investigation of surgery specific, drug concentration related, population specific and/or time-varying covariates of opioid requests and pain events.

Conclusions: A framework has been developed based on RTTE modelling that may help improve future pain management by 1) Identification of surgery specific patterns in pain events and 2) Evaluation of concentration related effects of opioids.

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Mats Karlsson I-47 Item response theory for analyzing placebo and drug treatment in Phase 3 studies of schizophrenia

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Objectives: In schizophrenia, the effects of placebo and drug treatment are often quantified using total PANSS scores. Treatment effects on the composite positive, negative, and general PANSS subscales have been quantified as well. In the current analysis, item response theory (IRT) is used to quantify treatment effects for each subscale based on PANSS item-level data.

Methods: Longitudinal data were available from 3 Phase 3 studies with a scheduled duration of 43 days, including 344 patients on placebo treatment and 948 patients on paliperidone with daily doses between 3 and 15 mg. Pre-dose data from 358 patients in comparator treatment arms were also available. Based on all baseline data, item characteristics curves (ICC) were constructed describing the probability of each score for each item as a function of an (unobserved) disease state that was modeled as a random effect, normalized to zero for the typical patient. For each patient different disease states were estimated for the positive, negative and general subscales. Changes in disease states over time were modeled using traditional placebo and drug effect models.

Results: On all 3 subscales, the placebo effect was best described by an asymptotic time-course model. The maximum placebo effect in the typical individual was highest on the positive subscale, for the general subscale the typical placebo effect was slightly lower, while on the negative subscale this maximum placebo effect was half that on the positive subscale. The drug effect was best described using a linear dose-effect relationship, in which the slope increased linearly in time from 0 to an estimated maximum at 43 days. For the typical patient, this maximum drug effect was about twice as high on the positive subscale, compared to the negative and general subscale.

Conclusions: In IRT analyses, changes in unobserved disease states rather than observed scores are modeled, complicating a direct comparison with previous findings. However, our results are in line with previous findings that both placebo and drug treatment most strongly improve positive schizophrenia symptoms.

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Mads Kreilgaard I-58 Study design optimization of a morphine analgesia trial using PKPD modelling and simulation

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Objectives: Morphine is the most commonly used opioid to alleviate moderate-severe pain [1]. For patients with gastrointestinal pain, rectal administration of morphine may be a feasible route to increase analgesic efficacy through central and local activation of opioid receptors. In order to select an optimal rectal dose for morphine in a forthcoming study, a population PKPD model was developed based on a pilot study in healthy volunteers undergoing experimental pain stimulation in order to select an optimal morphine rectal dose in a forthcoming study using simulations.

Methods: Ten healthy male volunteers were administered morphine, 2 mg IV or 10, 15, 20 mg rectally in a cross-over design on four different occasions. Ten blood samples were drawn in a sampling matrix design between 0-3 h for LC/MS/MS quantification of morphine in serum. During the same time period, the subjects were exposed to painful muscle pressure stimulation with a pneunomatic cuff algometer until moderate pain level (score 7 on a VAS where 5 is minimal pain and 10 unbearable pain). The PKPD model was developed in a sequential approach based on morphine plasma concentrations and muscle pressure tolerance scores over time, respectively, using NONMEM 7.2 and the First order conditional estimation method with interaction (FOCE-I). In the final model, PK and PD data were fitted simultaneously. Body weight was investigated as a covariate on the PK parameters. Model discrimination and evaluation were based on goodness-of-fit plots, visual predictive check, parameters precision, reduction in, objective function value and scientific plausibility. Based on the final PKPD model, simulations were performed in order to find an optimal dose matching criterias of ~ 15% peak response from baseline with morphine plasma levels

Results: A two-compartment model with first-order elimination best described the disposition of morphine. One Erlang-type absorption transit compartment [2] with first order rate constants (k_a and k_{tr}) best described the rectal absorption of morphine. The final PK model included allometric scaling of all clearance and volume parameters using body weight. The pain tolerance scores were best described by a direct log-linear model relative to morphine concentration. The model suggesting linear PK of morphine at rectal doses between 10-20 mg with a maximum increase in pain tolerance of 12% increased pain tolerance from baseline at the highest dose. Simulations from the PKPD model, suggested that ~15% median peak response could be obtained at a rectal dose of 30 mg, where the typical value for the predicted maximum morphine plasma concentration was 17 ng/mL (95% prediction interval: 6-36 ng/mL).

Conclusions: A non-linear mixed effect model was developed that adequately described morphine PK after IV and rectal administration, and the link to analgesia in healthy volunteers. The model predicted that a rectal morphine dose of 30 mg should provide target PK and PD response for a forthcoming study.

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Celine M. Laffont II-02 Population PK modeling and simulation to support dose selection of RBP-7000, a new sustained-release formulation of risperidone, in schizophrenic patients.

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Objectives: RBP-7000 is a sustained-release formulation of risperidone being currently developed for the treatment of schizophrenia. RBP-7000 has been designed for once-monthly subcutaneous injection in order to address compliance issues associated with risperidone oral intake. The objective of the present work was to guide RBP-7000 dose selection for future Phase III trials and to evaluate potential advantages of RBP-7000 over existing long-acting injectable antipsychotics. Our work is based on a modeling and simulation approach integrating competitor data from the literature.

Methods: A population pharmacokinetic (PK) model of RBP-7000 was developed to jointly describe the PK of risperidone and 9-hydroxyrisperidone after single or multiple doses of RBP-7000 (60, 90, or 120 mg) in 90 clinically stable schizophrenic patients. Active moiety (risperidone + 9-hydroxyrisperidone) plasma concentration-time profiles were simulated using this model for repeated administrations of RBP-7000 at 60, 90 and 120 mg. The simulated profiles were compared to the published data of Risperda® Consta® (risperidone long-acting injection [RLAI]; 25 and 50 mg), administered every two weeks, or Invega® Sustenna® (paliperidone palmitate [PP], 50 and 100 mg equivalent paliperidone) administered once per month [1].

Results: RBP-7000 data were well described by the population PK model. The simulations indicated that the dose of 90 mg of RBP-7000 provided similar active moiety exposure to 25 mg of RLAI under steady-state conditions, and that 60 and 90 mg of RBP-7000 provided similar active moiety plasma levels at steady-state compared to PP at 50 and 100 mg equivalent paliperidone, respectively. RBP-7000 reached effective concentrations immediately after the first administration. Thus, RBP-7000 did not seem to require any loading dose or supplementation with oral risperidone as required for PP and RLAI, respectively.

Conclusions: The results provide useful information regarding target RBP-7000 dose levels and suggest potential benefits of RBP-7000 compared to other long-acting antipsychotics.

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João Abrantes III-01 A repeated time-to-event model for epileptic seizures in patients undergoing antiepileptic drug withdrawal during Video-EEG monitoring

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Objectives: Video-electroencephalography (VEEG) monitoring is the gold standard for diagnosis of patients with seizure-related disorders. The aims of this study were to develop a repeated time-to-event (RTTE) model for the occurrence of epileptic seizures during VEEG, and to explore clinical information as predictors of the occurrence of seizures.

Methods: A retrospective analysis was carried out with data collected from epileptic patients submitted to VEEG at the Hospitals of the University of Coimbra, Portugal (1998-2005). To stimulate the occurrence of seizures during the VEEG, a drug discontinuation protocol was followed where drugs were withdrawn in a sequential fashion. To describe the time to occurrence of seizures, a parametric survival model defined in terms of hazard was fit to the data using NONMEM 7.3 [1]. Initially, the event distribution was identified. Thereafter, the number of anti-epileptic drugs (AEDs) each patient was taking during the study period was assessed as a time-varying covariate. Finally, an exploration of other covariates (age, sex, body weight, type of epilepsy, location of the epileptogenic focus) was done. The predictive performance of the model was evaluated with Visual Predictive Checks of the Kaplan Meier curves [2].

Results: Data from 111 inpatients were analysed (12-64 years) of which 81 experienced at least one epileptic seizure. The mean evaluative period was ~161 hours and the median number of seizures per patient was 2 (range 0-16 seizures). The RTTE data were best described by a Weibull distribution with parameters estimated independently for the first and for subsequent events. Inclusion of the change in the AEDs on the baseline hazard improved the model statistically significantly ($p<0.001$) implying an increasing risk for a seizure with a decreasing number of AEDs. The relationship was allowed to differ for the first event and repeated events. Patients with extra-temporal lobe epilepsy were found to have a higher risk for having a seizure ($p<0.05$) compared with patients with temporal lobe or generalized epilepsy.

Conclusions: A parametric RTTE model including the effect of number of AEDs and allowing for a difference in the distribution function of events for the first and for the subsequent seizures, described the data well. Patients with extra-temporal lobe epilepsy were found to have a higher risk of experiencing a seizure.

Acknowledgments: Leonardo da Vinci programme T4CD by the University of Coimbra.

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Oliver Ackaert III-02 Quantification of the effect of AZD5213 on sleep in subjects with Alzheimer's disease or mild cognitive impairment using a two state Markov model

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Objectives: H_3 antagonists have been extensively investigated for the (symptomatic) treatment of cognitive disorders, such as Alzheimer's disease (AD) or mild cognitive impairment (MCI). H_3 antagonists are effective across multiple cognitive domains (attention, memory) in preclinical studies at high receptor occupancy. However, administration of this class of drug in man is often accompanied by alterations in sleep patterns. This may be the result of enhanced histamine release during prolonged H_3 receptor occupancy (extending into the night). Therefore, in a Phase IIa study in patients with mild AD and MCI the effect of AZD5213, a novel and highly selective histamine H_3 antagonist, on sleep was quantified.

Methods: 81 subjects with mild AD or MCI were randomized in this double-blind, parallel group, placebo-controlled study of 4 weeks of treatment of three different doses of AZD5213. Repeated, nightly polysomnography (PSG) assessments were conducted at baseline, Week 2 and Week 4. During the PSG the sleep state per 30 second epoch was reported. This highly correlated longitudinal data was analyzed using a Markov modeling approach, in which two states were considered, WAKE and SLEEP with the latter obtained by merging the states REM, Sleep Stages 1, 2, 3 and 4.[1] It was investigated if placebo and/or modeled AZD5213 concentration influenced the intensity of acquisition (u) and clearance of sleep (v).

Results: Both u and v changed over time with a change in the ratio between the two intensities over time. No placebo effect was identified, while the drug concentration decreased u and v according to a sigmoid E_{max} and a log-linear relationship, respectively. AZD5213 plasma concentrations inhibited transitions to sleep more markedly than transitions to wakefulness. Simulations for various doses (low to high) at steady state (Week 2 and 4) demonstrated that overall time awake increased with increasing dose with a maximum effect at doses above medium strength.

Conclusions: The developed two-state Markov model adequately described and predicted the sleep pattern following QD administration of placebo and AZD5213 at the different occasions. Simulations showed a dose-related increase in the total time awake during the night and increased wakefulness appeared to be associated with receptor occupancies above 70% during the entire night.[2]

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Ricardo Alvarez III-04 Differences in response to scopolamine between young and elderly healthy adults using a modelling approach: reduction in the central cholinergic system in the elderly?

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Objectives: Scopolamine is a non-selective, muscarinic receptor antagonist that is used in a cholinergic challenge test for cognitive impairment. The test induces memory impairment similar to that seen in dementia or psychiatric diseases. Enhanced sensitivity to scopolamine in elderly has been attributed to a subclinical neuronal cholinergic reduction [1] which has led to dose reduction for this population [2]. The objective of this study was to describe the pharmacokinetics (PK) and pharmacodynamic (PD) effects of scopolamine in subjects in a broad age-range to determine the age-related sensitivity to the drug.

Methods: Data were obtained from four studies performed at CHDR where scopolamine was intravenously infused (15 minutes infusion of 0.5 mg in healthy adults and 0.3 mg in healthy elderly). A population PK-PD analysis was performed using a non-linear mixed effect modelling approach with NONMEM [3]. 139 subjects participated with a mean age of 39 years (min 18; max 78). Three neuro-cognitive PD markers were selected from the NeuroCart test battery: adaptive tracker performance, saccadic peak velocity and the alpha power of the EEG.

Results: A two-compartment PK model driving an indirect response model via an effect compartment best described the observations for all parameters. Clearance of scopolamine was linearly correlated to age and the body weight of the subjects and therefore used as a covariate. For all three PD markers, sensitivity to scopolamine (determined by the individual EC50 parameter estimates) showed no decrease with increasing age.

Conclusions: The PD effects in healthy subjects could be solely contributed to age-dependent differences in exposure rather than age-related hypersensitivity to scopolamine.

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Irina Bondareva III-19 Population modeling of steady-state pharmacokinetics of carbamazepine (CBZ) and its epoxide metabolite (CBZE) from therapeutic drug monitoring (TDM) data

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Objectives: CBZ is one of the most widely used antiepiletptic drugs for the treatment of partial and tonic-clonic seizures. Its main metabolite CBZ-10,11-epoxide is known to have antiepileptic properties similar to those of CBZ itself. The objective of the study is to develop a model of CBZ and its main metabolite (CBZE) pharmacokinetics (PK) and to estimate the model parameters from TDM data of adult epileptic patients on chronic CBZ – monotherapy.

Methods: Patient data of CBZ and CBZE monitoring were routinely collected in the Department of Pharmacokinetics of the Research Center of Neurology, Russian Academy of Medical Science. CBZ and CBZE levels were simultaneously measured by gas - chromatography - mass spectrometry. The assay error pattern was used as: SD=0.1+0.1C (where SD is standard deviation of the assay at measured concentration C). The nonparametric population PK analysis was performed using the Pmetrics based on a compartmental model with first-order absorption and linear elimination kinetics for both CBZ and CBZE. This study included 52 patients (40.8±14.3 years) for whom at least one pair of two measured serum levels of CBZ and CBZE (peak – trough strategy) related to CBZ dosage was available.

Results: Great interindividual variability of both CBZ and CBZE level to daily dose ratios was observed. Serum CBZE concentrations were 8 – 35% those of the parent drug. The CBZ:CBZ ratio increased for peak versus trough concentrations (the mean difference = 1.4%, p=0.03). The interindividual variability of CBZE:CBZ concentration ratio was estimated as 46%. The estimated CBZ and CBZE population PK parameter values were in good agreement with those obtained earlier for the steady-state CBZ population PK model for epileptic adult patients [1].

Conclusions: The study demonstrated wide interindividual variability in CBZ and CBZE pharmacokinetics and the need for individualizing of CBZ dosage regimens. Estimation of individual PK parameters of both drug and its active metabolite might help to optimize CBZ therapy in epileptic patients based on TDM data.

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Jae Yong Chung III-40 Ethnic difference of ADAS-Cog Placebo Response in Patients with Alzheimer's Disease

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Objectives: Alzheimer's Disease progressively decreases cognitive function and Alzheimer Disease Assessment Scale (ADAS-Cog) is the standard score used to assess cognition in clinical trials. Better understanding of the time course of placebo response and natural disease progression and their covariates would be essential for designing better clinical trials. In addition, ethnic difference may exist in the placebo response. The aim of this work is to investigate the ADAS-Cog placebo response in Alzheimer's disease and evaluate the effect of Asian ethnicity and other covariates by population modeling approach.

Methods: Data were obtained from an open database of the CAMD (Coalition Against Major Disease) Alzheimer trial database run by Critical Path Institute. In the placebo arms of 5 clinical trials, 63 Asian and 69 African patients were eligible and study-matching Caucasian patients (n=150) were randomly selected. ADAS-cog were modeled to investigate the disease progression and placebo response as a function of time. Nonlinear Mixed Effects Modelling Approach was applied to these data using NONMEM V7.2. The following models were explored:

ADAS = ADAS0 + S*t – A* (1 – exp(-k*t)) + ε, where ADAS0=ADAS-Cog at baseline, S=disease progression slope, A=magnitude of placebo contribution, k=onset rate of placebo response, ε=error. For each parameter, between-subject variability was tested and covariate analysis was investigated.

Results: The covariate analysis showed that the effects of ethnicity, baseline age, and participation duration on disease progression rate were significant. Goodness-of-fit plots and the visual predictive check showed a good adquacy between observed data and predicted (simulated) data. Maximum placebo effect was estimated to be 8.55. The disease progressoin slope of Caucasian (0.018/day) was 50% greater than that of Asian (0.012/day). The confidence intervals produced by non-parametric bootstrap analyses confirmed the significance of the difference. The slope was multiplied by (1 – 0.0373*(Age – 75)) and (1 – 0.00089*(participation duration – 546)). The covariate effects on placebo response could not be identified.

Conclusions: The model adequately describes ADAS-cog progression in patient with placebo treatment. Our results suggest that the natural disease progression can be slower in Asian than Caucasian and inversely correlated with age at baseline, and slower in patients participating longer period. These findings could help optimize the design of clinical trials for Alzheimer's disease.

Shinji Shimizu IV-09 PBPK modeling of CNS distribution for risperidone and its active metabolite, paliperidone

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Objectives: Prediction of exposure level in the central nervous system (CNS) is critical during the development of CNS-targeted and non-targeted drugs[1, 2]. In fact, a number of approaches have been proposed to estimate CNS exposure, such as in vitro cell-line system, determination of concentration ratio of brain to plasma at steady state. However, in terms of translation from in vitro to in vivo or animal to human, the information on those preclinical data still remains to be fully interpreted. Recently, much attention has been drawn to physiologically-based pharmacokinetic (PBPK) modeling since this approach can potentially simulate drug concentrations in human tissues based on in vitro experimental data, in vivo animal PK data, or combination of them, in a mechanistic way[1, 2, 3]. The objective of this study is to develop a PBPK model to describe CNS drug distribution of risperidone and its active metabolite, paliperidone. In addition, an impact of P-gp functioning on the CNS entry of those drugs is assessed[4].

Methods: In our in vivo experiment, the microdialysis rat model was used to provide serial samples of plasma, brain extracellular fluid (ECF), and cerebrospinal fluid (CSF). Rats received risperidone or paliperidone intravenously after pretreatment of P-gp inhibitor, tariquidar (TQ). NONMEM analysis was carried out in a stepwise approach. As a first step, plasma PK model was developed for both compounds. As a second step, resulting plasma PK parameters were fixed and then used for the development of CNS distribution model. Physiological parameters, such as flow of ECF and CSF, and volume of each CNS site, were used to construct the CNS model.

Results: In visual predictive check (VPC), the proposed model well described the observed PK profile in plasma and CNS for both risperidone and paliperidone. Additionally, differences in PK between with and without TQ treatment were nicely captured.

Conclusions: The proposed PBPK model together with the microdialysis technique allowed us to describe CNS distribution as well as to quantify P-gp clearance for both risperidone and paliperidone in rats.

Amit Taneja IV-24 Development of a mechanism-based pharmacokinetic-pharmacodynamic model of prolactin response following administration of D2 antagonists in rats

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Objectives: Schizophrenia is characterized by dopamine dysregulation. Treatment with D_2 antagonists results in side effects including prolactin release, which manifests clinically as weight gain, gynaecomastia and decreased libido in males. In this project we evaluate mechanism-based PKPD models [1,2] which can describe the time course of prolactin (PRL) concentrations in plasma (PD) in rats following administration of D_2 antagonists.

Methods: Plasma concentration profiles of risperidone and prolactin were obtained following single dose administration via oral (n=39) or subcutaneous (n=61) routes in male Sprague-dawley rats who received a dose of 0.01, 0.04, 0.16, 0.63 or 2.5 mg/kg or vehicle. Plasma concentrations of risperidone and its active metabolite paliperidone were simulated using a two-compartment model with sequential absorption [3]. A mechanistic PKPD pool model was used to describe the prolactin time course. This comprises of the following sub-models:

-A pool model describing prolactin synthesis, storage in lactotrophs, prolactin release into plasma and elimination from plasma.

-A drug effect component quantifying the effect of D_2 antagonists on prolactin release.

Results: We obtained the following model parameter estimates: baseline prolactin level 3.59 ng/ml, rate constant for the release of prolactin from the lactotrophs 0.46 /h, rate constant for prolactin elimination from the plasma 4.84 /h. The drug effect was parameterised by using an E_{max} function. Our results indicate that peak plasma prolactin secretion induced by risperidone is greater than 250 ng/ml. An E_{max} and a linear function were tested to parameterise the positive feedback effects of prolactin. Model performance was slightly better with an E_{max} function.

Conclusions: Estimated values for baseline prolactin levels and rate constant for the release of prolactin were comparable to the values reported by Stevens et al (6.2 ng/ml and 0.6 /h, respectively). However, alternative parametrisation will need to be evaluated prior to confirming these results. In addition, the results suggest that, multiple dosing is necessary in order to describe homeostatic feedback mechanisms with single doses.

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Paulo Teixeira IV-25 Population Pharmacokinetic Model of Valproic Acid in Adult Patients

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Objectives: The main goal of this work was to develop an updated population pharmacokinetic model to identify and quantify the influence of demographics, clinical and treatment factors on the clearance (CL) of valproic acid (VLP) in adult patients.

Methods: Serum concentrations of VLP were taken from patients aged 15-84 years old, who had been treated with sodium valproate. These patients were included in the TDM program, conducted in the University Hospital of Salamanca over the last 20 years. After applying the inclusion/exclusion criteria previously established, the final database included 868 serum concentrations from 411 patients. Pharmacokinetic analysis was performed with NONMEM V7.2 (FOCEI) considering a one-compartment model, fixing the absorption constant and volume of distribution at 4.1 h^{-1} and 0.20 L/kg, respectively[1-3]. Proportional error models were assumed to describe interindividual and residual variabilities. The analysed covariates were: weight (WGT), age, gender (SEX), and concomitant treatment with carbamazepine (CBZ), clobazam (CLB), clonazepam (CLO), phenobarbital (PHB) phenytoin (PHT), lamotrigine (LTG), topiramate (TOP) and vigabatrin (VIG).

Results: The covariates with significant influence on CL_{VLP}/F were: WGT, SEX and concomitant treatment with CBZ, PHB, PHT, LTG and VIG. LTG was excluded in the backward elimination process ($p < 0.01$). The covariate SEX was also eliminated in the final model because of the low clinical significance (< 15 %). The proposed final model for CL_{VLP}/F was as follows:

$$CL_{VLP}/F\ (L/h) = 0.58\times((WGT/70)^{0.58})\times(1.44\times CBZ)\times(1.23\times PHB)\times(1.39\times PHT)\times(1.44\times VIG)$$

$w^2 = 0.055$ (*shrinkage*: 16 %)
$s^2 = 0.033$ (*shrinkage*: 21 %)
The standard estimation error was lower than 11 % for all parameters.

VIG does not undergo biotransformation or binding to plasma proteins[2], however we found that this drug significantly increases CL_{VLP}/F. Its inclusion/exclusion in the model did not affect the influence (type and extent) of the others covariates on the CL_{VLP}/F. This is why this drug was maintained in the final model despite the lack of physiological justification of this fact.

Conclusions: The population pharmacokinetic model developed for VLP in adult patients includes WGT and the concomitant administration of CBZ, PHB, PHT and VIG. More studies are required to verify the causes and the true extent of the interaction discovered between VIG and VLP.

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Iñaki F. Trocóniz IV-30 Population pharmacokinetic/pharmacodynamic modelling of the analgesic and pupillometry effects of axomadol and its O-demethyl metabolite in healthy subjects

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Objectives: To characterize the PKPD properties of the active components of axomadol (GRT0151Y) quantifying their contribution to the analgesic and pupillometry effects.
Racemic axomadol is a centrally active analgesic agent with opioid agonistic properties and inhibitory effects on the monoamines reuptake. The opioid action is related to the (+)-enantiomer of the O-demethyl metabolite, whereas the monoamine reuptake inhibition is exerted by the (-) enantiomers.

Methods: Data from two clinical trials were used to perfom the analysis. Healthy volunteers (n=74) received either placebo or axomadol orally at doses of ranging from 75 to 225 mg following multiple dosing regimens. Blood samples were withdrawn at selected times to quantify the plasma concentrations of the two enantiomers of axomadol and its metabolite. Pharmacodynamic responses (initial pupil diameter and cold pressor test) were also measured at specific times during the trials.The population analysis was performed with NONMEM 7.2.

Results: The kinetics of the parent drug and its metabolite could be simultaneously described using a PK model including an extra compartment resembling the liver, from which the metabolite is formed, and from which the drug distributes to the central compartment. The current analysis confirms that within the dose range studied axomadol and its O-demethyl metabolite show linear pharmacokinetic characteristics. Administration of axomadol elicited significant effects on both pharmacodynamic endpoints with respect to placebo. (-)-parent compound elicited a plasma concentration dependent increase in pupil diameter that could be characterize by an EMAX model, on the contrary the (+)-O-demethyl metabolite decreased the pupil diameter as a linear function of the predicted effect site concentrations. An additive model integrating both type of response described adequately the net effects. For the case of the Cold pressor test, the use of the plasma concentration of the (+)-metabolite provided an adequate description of the response data.

Conclusions: The PKPD analysis performed in the current evaluation based on plasma concentration and biomarker data after oral administration of racemic axomadol has allowed to extract and quantified the PKPD properties of the active compounds. Those properties were in accordance with the known mechanisms of action, namely opioid agonism and inhibitory effects on the reuptake of NA and 5-HT monoamines norepinephrine (NA) and serotonin (5-HT).

Sven van Dijkman IV-35 A PKPD Hidden Markov Model for Lamotrigine in all age groups

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Objectives: Due to high variability in pharmacokinetics, pharmacodynamics, disease progression and maturation, clear dosing recommendations regarding anti-epileptic drugs are often not available. A hidden Markov model is proposed, that incorporates the pharmacokinetic maturation over all age ranges and takes into account the disease progression. Dosing recommendations are made to improve the clinical management of this disease when treating paediatric patients with lamotrigine.

Methods: Clinical trial data in patients using lamotrigine alone or in combination with other drugs were used. Datasets included both sparse and rich steady-state PK samples across a wide range of ages (from 01 month to 18 years) and types of epileptic seizure. Drug concentrations were first used to fit a PK model that included the effects of weight and maturation. The resulting PK model was subsequently used to simulate systemic exposure, as determined by AUCs. These results were used as input for a Hidden Markov model implemented in NONMEM [2], in which changes in transition rates and probabilities of seizure occurrence were evaluated.

Results: The population PK model showed good performance with adequate accuracy and precision. The effect of weight was added allometrically and the inclusion of maturation on clearance significantly improved model fit. The hidden Markov model provided a good description of the cumulative seizures over time and the trend in seizures, with limited misspecification of active and inactive states. Transition probabilities between states were found to be significantly altered by both placebo and treatment effects, with epilepsy type and age as covariates.

Conclusions: Markov processes appear to better describe seizure frequency in epilepsy [1,3], as compared to standard time to event analysis. In addition, the use of a hidden Markov model seems to provide a more robust description of the process, when compared to Markov. It can be anticipated that dosing recommendations may be derived for children which take into account the dynamics of disease.

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Eline van Maanen IV-37 Integrating tracer kinetic data with absolute protein concentration measurements in a systems pharmacology model. Application to the APP pathway in CMP rhesus monkeys.

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Objectives: Integrating biomarkers from different analytical tools to gain understanding of the underlying biological system in a comprehensive model can result in technical challenges. An example of such is discussed for the integration of data from tracer kinetic studies with absolute protein concentration measurements of the amyloid precursor protein (APP) pathway. Biomarkers of interest include fraction labeled total amyloid β (Aβ), fraction labeled secreted APP β (sAPPβ), fraction labeled sAPPα and absolute protein concentration measurements (Aβ40, Aβ42, sAPPβ, sAPPα). The objective was to establish a systems model characterizing APP metabolite responses to BACE inhibition, that could account for tracer dynamics throughout the APP pathway and therefore could aid the interpretation of the tracer kinetic data.

Methods: Dose-ranging, biomarker and pharmacokinetic (PK) data obtained from CSF in cisterna-magna-ported (CMP) rhesus monkeys receiving single doses of BACE inhibitor were available. Absolute protein concentrations were determined by enzyme linked immunosorbent assay (ELISA). Plasma enrichment labeled leucine (6C13) and fraction labeled proteins were determined by stable isotope labeling kinetics (SILK) [1]. Nonlinear mixed effects modeling (NONMEM) was used to analyze (A) the time course of the changes in APP metabolites on the basis of the underlying biological processes, using a comprehensive biomarker model; (B) the plasma tracer enrichment over time; (C) and the time course of changes of fraction labeled proteins following BACE inhibition by incorporating tracer dynamics in the model.

Results: (A) A comprehensive biomarker model quantified the response of all 4 biomarkers to BACE inhibition, using one drug effect term. (B) A two pool model related tracer infusion to the measured enrichment. (C) Tracer dynamics throughout the APP pathway was built-in the model, integrating information from the PK, plasma enrichment and the pharmacodynamics *(ELISA and SILK)* of the BACE inhibitor across time points, doses and endpoints. This yielded pertinent information on the dose response relationship, the dynamics of APP metabolite responses (sAPPβ, sAPPα, Aβ) and the similarities and differences in the responses as measured by ELISA and SILK.

Conclusion: The systems model integrating tracer kinetic data with absolute protein concentration measurements enabled a more informed interpretation of the tracer kinetic study and the APP pathway.

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Marc Vandemeulebroecke IV-40 Identifying neuropsychological domains with high information on early signs of cognitive decline: An application of Item Response Theory in the Basel Study on the Elderly

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Objectives: The goal was to investigate which cognitive domains carry most information in the earliest stages of cognitive decline. This may be helpful in the development of disease-modifying drugs against Alzheimer's disease, which must intervene before the onset of clinical symptoms.

Methods: Following the idea of Ueckert et al. [1], Item Response Theory was applied to 14 variables of the CERAD-NAB, its additions (phonemic fluency; Trail Making Test, parts A and B), and the CVLT, based on data from 1,101 cognitively healthy elderly subjects and two subjects with probable AD (39% women; mean age ± sd = 69.9 ± 8.28 years) of the BASEL study. The model was implemented in a Bayesian framework with non-informative priors. The estimated discrimination parameters and Fisher information were used to assess the information content of the different component tests.

Results: 'CERAD-Word List Learning' and 'CVLT-Word List Learning' as well as 'CERAD-Word List Delayed Recall' and 'CVLT-Word List Long Delay Free Recall' carried most information in the BASEL sample (17.4%, 16.2%, 15.1% and 11.5%, respectively, of the total amount of information). CVLT variables did not carry more information than corresponding variables of the CERAD-NAB. 'Trail Making Test (Part B)', 'CVLT-Word List Recognition Discriminability', 'CERAD-Word List Recognition Discriminability', 'Mini Mental Status Examination (MMSE)' and 'Semantic Fluency' carried little information overall, with the word list recognition tasks and the MMSE being informative in the low ability range (only). 'Phonemic Fluency', 'CERAD-Figures-Delayed Recall', Trail Making Test (Part A), 'Boston Naming Test', and 'CERAD-Figures-Copy' carried almost no information.

Conclusions: By application of Item Response Theory in the Basel Study on the Elderly, it was possible to quantify the information contribution of individual test items to the CERAD-NAB and CVLT neuropsychological test batteries in this study. Verbal episodic memory as assessed by word list learning and recall tasks carried most information. Hence, this may be a promising domain for the detection of earliest signs of cognitive decline in initially healthy subjects.

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Nieves Velez de Mendizabal IV-41 Analysis of Sleep Changes Induced by Citalopram: A Population Approach

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Objectives: To develop a population kinetic-pharmacodynamic (KPD) model that describes the pattern of sleep and quantifies the sleep changes in Wistar rats after different oral doses of citalopram.

Methods: Citalopram was administered orally (PO) to 91 Wistar rats at different doses: vehicle (n=17), 0.3 (n=8), 1 (n=11), 2.5 (n=8), 5 (n=11), 10 (n=10), 30 (n=18) and 60-mg/kg (n=8). Citalopram and n-desmethylcitalopram concentration measurements were not available in this study, therefore simulated profiles were used derived from a previously published PK model by Velez de Mendizabal et al. [1] for Wistar and Sprague-Dawley rats and used as input to the PD model. No Inter-subject variability was included in those profiles, although weight was taken into account to adjust parameters. Three dependent variables (DV) were defined for estimation. They represent the accumulated minutes in AWAKE, NREM and REM stage. These three DVs were simultaneously modelled during both the baseline (no treatment) and the citalopram/vehicle treatment period. This model was developed in three steps: (i) baseline, (ii) handling effect and (iii) drug effect. The analyses were performed using NONMEM version 7.2 (Icon Development Solutions, Hanover, Maryland). The First Order Conditional Estimation method with the INTERACTION option was used for parameter estimation.

Results: The accumulated number of minutes in AWAKE, NREM and REM stages were described using a 3-compartment model, one per stage, defined by three inter-related zero order rate functions (minutes per hour). Administration of citalopram produced changes in those rates resulting in a new dynamic re-distribution of the accumulated minutes in AWAKE, NREM and REM stages. However, REM sleep is the more affected stage by means of a strong inhibition.

Conclusions: The KPD model developed here describes sleep architecture with and without citalopram treatment, and quantifies the strong REM inhibition effect at multiple dose levels in rats. This population analysis was carried out with the lack of the actual citalopram and n-desmethylcitalopram concentrations. The PD model part of the model (baseline, handling effect) can be also applied for drug effect evaluations of other sleep changing compounds.

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Shaonan Wang IV-44 Exposure-response analysis of Axomadol in patients suffering from hip and/or knee-joint osteoarthritis pain

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Objectives: Axomadol is a central analgesic, antinociceptive agent that was developed for the management of acute and chronic pain of moderate to severe intensity. In this dose finding trial, the primary endpoint was a numerical rating scale (NRS) assessing patient's pain on a scale from 0="no pain" to 10="pain as bad as you can imagine". The objective of the study was to explore the relationship between Axomadol concentrations and NRS pain scores assessed on a daily basis via different modelling approaches.

Methods: Data from a randomized, placebo-controlled, double-blind, phase IIb, parallel-arm study assessing the analgesic efficacy of three dose levels of Axomadol (50 mg, 75 mg, 125 mg bid) in patients with chronic hip and/or knee-joint osteoarthritis were modelled. A population PK model was previously developed [1]. The NRS pain scores could be considered as continuous or categorical data and were modelled in NONMEM7.2 [2] by three different approaches: a continuous model assuming normal distribution, a logit model and a truncated generalized Poisson model [3]. In all three approaches, a time/placebo effect component characterized by an exponential decay function as well as a drug effect component were included.

Results: All three approaches could be successfully implemented in NONMEM and adequately described the data. Models with a treatment-specific time/placebo effect fitted the data better than models using shared time/placebo effect. An Emax function best described the drug effect component. All three approaches were capable of predicting the mean NRS pain scores, as the predicted mean values agreed with the observed ones.

Conclusions: In this study, we have shown that i) Axomadol exposure drove the efficacy as reflected in the reduction of the NRS pain scores; ii) The logit and truncated generalized Poison models could be used to model NRS pain scores from a real dose finding clinical trial.

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Li Zhu IV-57 Population Pharmacokinetic/Pharmacodynamic Models for the Heart Rate Effects of BMS-820836, a Triple Monoamine Reuptake Inhibitor, in a Thorough QT Study

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Objectives: To develop PK/PD models to characterize the exposure and heart rate (HR) relationship in a thorough QT (TQT) study for BMS-820836, a highly potent and selective triple monoamine reuptake inhibitor for treatment-resistant depression.

Methods: 24-hour ambulatory HR and time-matched PK data were obtained from a double blind, placebo and positive-controlled, parallel group TQT study in 172 healthy subjects. Four parallel groups included 2 BMS-820836 treatment groups (2 and 4 mg), and 2 nested-crossover groups of placebo and 400 mg moxifloxacin single dose. Steady-state PK of BMS-820836 was achieved following a 14-day up-titration scheme. The PK/PD models were developed sequentially. First the population PK model (PPK) was developed based on a pooled dataset that also included 5 additional Phase 1 studies. Individual post-hoc parameter estimates were obtained and were used in the subsequent modeling of HR response data. The non-linear mixed-effects modeling approach was used and estimation was done with the first order conditional estimation with the interaction option implemented in NONMEM V7.2 [1]. Inter-subject variability in the PPK model was described with an exponential function. The residual variability was described with a combined error model in the PPK model and an additive error model in the PD model.

Results: Plasma disposition of BMS-820836 within a dosing interval can be adequately described by a two-compartment model. Absorption was modeled with a zero-order release followed by first-order absorption process. Age, gender and baseline body weight were identified as statistically significant covariates for the PPK model. HR change from baseline was exposure dependent and was modeled with an indirect response model. The drug effect on HR was best described with the use of a stimulatory Emax function on the production rate parameter Km. Circadian rhythm in HR response was modeled with 2 periodic cosine functions. Placebo effect was incorporated in the model. Individual HR profiles and distribution of data were well captured for both dose groups as well as the placebo subjects. Simulations were performed to estimate HR effects expected with unstudied dosing regimens.

Conclusions: The PK/PD models adequately described the disposition of BMS-820836 and its effect on HR. The models provide a useful tool to inform further clinical assessment of the cardiovascular effects of the drug.

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Petra Jauslin I-39 Comparison of post-prandial glucose control by two GLP-1 receptor agonists (lixisenatide and liraglutide) in type 2 diabetes

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Objectives: To develop mechanistic meal test models for lixisenatide, a short-acting prandial GLP-1 receptor agonist [1], and liraglutide, a long-acting one, in order to compare their mechanisms of action and the relative contributions of their respective effect sites to their overall post-prandial glycaemic control.

Methods: Glucose, insulin and glucagon data during meal tests from 143 patients were analysed. The previously published integrated glucose-insulin (IGI) [2] model, developed in NONMEM [3], was extended with a glucagon component. A K-PD [4, 5] analysis of the test drug's effects on selected parameters (insulin secretion, gastric emptying, hepatic glucose output, glucagon production and insulin sensitivity) was performed. Sites of drug action were added one at a time. The best effect site was selected and all other sites were tested again until no further improvement of fit could be obtained by adding further effect sites.

Results: The IGI+glucagon (IGIG) model was able to adequately describe glucagon profiles in type 2 diabetic patients, capturing its most important interactions with the glucose-insulin system (glucose and insulin effects on glucagon production, glucagon effect on endogenous glucose production and meal effect on glucagon production). The drug-effect model structures for lixisenatide and liraglutide were similar: identified mechanisms of action included suppression of glucagon production and increase of insulin secretion, gastric emptying time and insulin sensitivity. Lixisenatide data were described by a combination of constant and dynamic effects: effects on gastric emptying, glucagon and, in part, insulin secretion were time-dependent. Liraglutide, owing to its longer half-life, exhibited stable drug effects over the test period. Simulations show that the increase of insulin secretion is the most important factor for lowering plasma glucose by liraglutide. For lixisenatide, the gastric emptying effect is most influential during the meal test. The glucagon-mediated effect on post-prandial glycaemic control was not substantial despite both compounds having a significant effect on glucagon production.

Conclusions: The same effect sites were identified for lixisenatide and liraglutide in the meal test situation. However, the relative importance of each effect site differed. Lixisenatide exhibited a profound effect on post-prandial glycaemia, mainly mediated by delaying gastric emptying, as reported for prandial GLP1 agonists.

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Yukyung Kim I-52 Metformin's glucose lowering effect in healthy volunteers receiving an oral glucose tolerance test

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Objectives: Although metformin is a widely used for the treatment of type II diabetes mellitus, only a few articles have reported the relationship among its plasma concentrations (PK), glucose-lowering effects (PD), and related covariates. This study investigates a model describing such relationship in metformin.

Methods: A total of 48 healthy Korean subjects were included in the analysis. For each subject, after an overnight fast, a 3-h oral glucose tolerance test (OGTT) was performed at 10 AM in Day 1 to obtain baseline glucose levels. Then, they received the 1st dose of metformin (1000 mg) at 8 PM. Next day, the 2nd dose of metformin (750 mg) was given at 8 AM, followed by the 2nd OGTT test conducted in a fasted state 2 hours after the 2nd dose. Metformin plasma concentrations were measured using LC-MS/MS. NONMEM 7.2 was used to analyze the data.

Results: Plasma concentrations of intrinsic glucose were described by a turnover model with negative feedback via a moderator controlling glucose homeostasis and those of extrinsic glucose from OGTT by one-compartment model, assuming intrinsic and extrinsic glucoses share disposition PK parameters. Then, metformin's PK was described by a 2-compartment model with 1st-order absorption and PD by an Emax model inhibiting both intrinsic glucose production and extrinsic glucose appearance rates in the plasma. Parameter estimates of glucose were 126 L/hr, 70.9 L, 82.1 mg/dL, 3.03 hr and 1.44 hr for clearance, volume of distribution, baseline level, rate constant for feedback site and absorption rate constant for extrinsic glucose, and those of metformin were 94.2 L/hr, 158 L, 243 L, 42.8 L/hr, 0.547 h^{-1} and 21,400 ng/mL for clearance, volume of distribution of central and peripheral compartments, intercompartmental clearance, absorption rate constant, and IC50 respectively. No covariate was found significant in metformin' PK or PD. These estimates yielded the baseline glucose production rate of 34.9 g/hr and the half-life of glucose for plasma and feedback site of 0.39 hr and 0.23 hr, respectively, and that of metformin 1.2 hr. The model performance was evaluated using visual predictive check.

Conclusions: Glucose concentrations from OGTT were well described by a turnover model with negative feedback and metformin's glucose lowering effect by inhibiting glucose production and appearance rates. No covariate was found significant. To better understand PK-PD relationship of metformin, a clinical study in actual patients is needed.

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Yan Ren II-53 Effect of fluticasone furoate treatment on cortisol circadian rhythm in healthy Chinese subjects

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Objectives: Fluticasone furoate (FF) is a novel corticosteroid with potent glucocorticoid activity. It has being developed as a potential steroid component in monotherapy and a once daily ICS/LABA combination for asthma and COPD. Cortisol levels in healthy Chinese male subjects before and after FF treatment were measured and characterized by a cosine model. The influence of FF on cortisol circadian rhythm was explored.

Methods: In a single centre, double-blind, placebo-controlled, four-way crossover, randomized, single and repeat dose study, FF at different doses (50, 100, 200 mcg) was administered in combination with 25 mcg vilanterol (VI) to evaluate the PK/PD profile, safety and tolerability in healthy Chinese male subjects. A total of 16 healthy subjects aged 18-45 years were randomized with the aim of achieving at least 10 evaluable subjects in each treatment period. Serum cortisol levels were measured on day 7 pre- and 1, 2, 4, 6, 8, 10, 12, 16, 24 hr post FF or placebo repeated dose. Time profiles of cortisol were described by circadian rhythm (cosine) functions.

Results: A model with two cosine terms and baseline could adequately characterize the endogenous cortisol circadian rhythm. Although data were limited (e.g., cortisol was not measured between 10 pm to 8 am), modeling results showed cortisol profiles consistent with results from previous publication [1]. FF concentrations, instead of FF doses, can be used as a covariate in the model. The effect of FF after repeat doses on cortisol lowering appears to have no delay.

Conclusions: This cosine model with direct FF effect reasonably captured the circadian rhythm of cortisol in healthy Chinese subjects.

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Clémence Rigaux II-56 Modeling HbA1c dynamics in type II diabetes mellitus in patients treated with GLP-1 receptor agonist lixisenatide

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Objectives: To extend a recently published disease progression [1] model for lixisenatide, a prandial GLP-1 receptor agonist [2], in order to explicitly account for 2H post prandial glucose (PPG) data for describing and predicting HbA1c over long term.

Methods: Fasting plasma glucose (FPG), 2H glucose excursion (GLUEX) data, defined as the difference between FPG and PPG, fasting serum insulin (FSI) and HbA1c data were collected in 5 phase II and III clinical trials. Data from another phase III trial were used for external validation. Observations from 2.470 patients were used. Data were analyzed with a non-linear mixed modelling approach using Monolix 4.1.3. and SAEM algorithm. FPG and FSI were described by the former semi-mechanistic model, while GLUEX was empirically modelled. HbA1c was then described with a turn-over model linked to FPG and PPG.

Results: An immediate drug effect was identified on GLUEX, with dose response modelled with an Emax function, leading to a predicted mean decrease of 2.8 mmol/L for a 20 µg QD lixisenatide dose. An additional reduction of 1 mmol/L accounted for a placebo effect. The model predicted a disease progression corresponding to a mean increase of 0.5 mmol/L after 24 weeks. Inter-individual variability was identified on baseline GLUEX value and on ED50, with baseline HbA1c and Asian race as covariates, and on the disease progression coefficient.

HbA1c synthesis was described as a linear function of FPG and GLUEX, combined with an elimination term. Inter-individual variability was identified on the FPG and GLUEX contributions coefficients, with baseline HbA1c, baseline FPG, and Asian race as covariates. GLUEX reduction (-2.8 mmol/L on average) accounted for about 3 times more than FPG reduction (-1.1 mmol/L on average) in the decrease of the HbA1c synthesis rate induced by lixisenatide.

Standard diagnostic tools, including external qualification procedure, showed an acceptable quality of fit of the data.

Conclusions: For up to 24 weeks, the model properly describes the therapeutic reduction of HbA1c levels and discriminates the relative contribution of lixisenatide effects on FPG and on PPG. This extended model of disease progression in type II diabetes adequately predicts the long term HbA1c therapeutic changes of a prandial GLP-1 receptor agonist, lixisenatide.

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Rikke Meldgaard Røge II-57 Modelling of Glucose and Insulin profiles in Patients with Type 2 Diabetes Mellitus treated with a GLP-1 analogue

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Objectives: In recent years several Glucagon-like peptide-1 (GLP-1) based therapies for the treatment of type 2 diabetes mellitus (T2DM) have been developed. GLP-1 analogues stimulate insulin secretion in a glucose-dependent manner, slow gastric emptying and decrease appetite, which leads to an improved glycaemic control. The aim of this work was to extend the previously developed semi-mechanistic integrated glucose-insulin (IGI) model [1] to include the effects of a GLP-1 analogue on glucose and insulin homeostasis in T2DM patients.

Methods: The data used for model development were from a single-center, randomized, placebo-controlled, double-blind, two-period, crossover trial, comparing the effect of steady-state liraglutide at three dose levels (0.6, 1.2, and 1.8 mg/day) versus placebo on the responses of fasting plasma glucose and post-prandial glucose, insulin, and gastric emptying in T2DM patients [2]. After one week of treatment at each dose level, an energy fixed meal tolerance test (MTT) was performed during which serum insulin and glucose profiles were obtained.

The IGI model, used in the analysis, consists of glucose and endogenous insulin compartments and control mechanisms in the form of effect compartments [1]. The model was extended to allow incorporation of the effect of liraglutide on glucose homeostasis. The data were analysed using NONMEM7.

Results: The IGI model was extended to describe the glucose profiles for T2DM patients treated with a GLP-1 analogue. The effect of the GLP-1 analogue on glucose homeostasis was incorporated in the model by including: 1) a stimulatory effect on insulin secretion, and 2) an inhibitory effect on glucose absorption, which was included to account for a delay in gastric emptying during the early phase after the MTT.

The predictive performance of the model was graphically evaluated by a visual predictive check (VPC). The VPC showed that the main trend of glucose and insulin was well captured by the model at all dose levels.

Conclusions: The IGI model was successfully extended to describe glucose homeostasis in T2DM patients treated with the GLP-1 analogue liraglutide. As other GLP-1 analogues have similar mode of action it is believed that the model can also be used to describe the effect of other analogues on glucose homeostasis.

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Trine Høyer Rose II-59 Dose-concentration-response modelling of inhibin B in controlled ovarian stimulation with FE 999049, a recombinant FSH derived from a human cell-line

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Objectives: A recombinant follicle stimulating hormone (FSH) expressed from a cell-line of human fetal retinal origin (PER.C6®), FE 999049, is currently under development at Ferring Pharmaceuticals and is intended to be used in infertility treatment for controlled ovarian stimulation. The objective of the present analysis was to characterise the FE 999049 dose-inhibin B-response using a semi-mechanistic model based approach. In addition the aim was to use the model to improve precision of inhibin B predictions, a potential marker of ovarian response to gonadotropin treatment for controlled ovarian stimulation, compared to estimates obtained with traditional statistical methods.

Methods: A semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model describing the FE 999049 concentration-time profile and inhibin B levels after multiple doses of FE 999049 was developed based on data from a phase II clinical study including 222 infertile women. The pharmacokinetic model development was supported by model results and parameters from a phase I study. The PKPD model structure was based on the underlying physiology for the hormonal dynamics of FSH and inhibin B in the reproductive endocrine system, and adjusted in accordance with the clinical study protocol and observed data. The model was implemented in NONMEM 7.2.0 and graphical presentations were performed in R.

Results: The FE 999049 pharmacokinetics were described using a one compartment model with first order absorption and a transit compartment for a delayed absorption. The endogenous FSH levels were not down-regulated in the women prior to stimulation and were therefore included in the model as an extra input to the central compartment. Using the total FSH concentration the PK model was linked to an indirect stimulatory response model for inhibin B levels with a negative feedback loop to the endogenous FSH production.

Conclusions: The semi-mechanistic PKPD model for the FE 999049 dose-inhibin B-response relationship was shown to improve precision of inhibin B prediction compared to when using an empirical dose-response model or confidence intervals obtained with traditional statistical methods.

Roberto Bizzotto III-18 Glucose Homeostasis Modeling: Improvement of the Insulin Kinetics Component

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Objectives: Models of glucose homeostasis are important for the development of anti-diabetic drugs. Several models have been developed (e.g. [1]); however, the complexity of the processes and the necessity of rich data sets has limited the possibility to account for all mechanisms relevant for glucose homeostasis. One neglected aspect is insulin kinetics, which has typically been assumed to be linear, in contrast to physiological evidence [2]. Aim of this work is to develop a model of insulin kinetics on a data set with a wide insulin span following stimulation of exogenous insulin secretion and endogenous insulin infusion.

Methods: Data were obtained from: A) a frequently-sampled combined hyperglycemic/hyperinsulinemic glucose clamp followed by arginine injection and exogenous insulin infusion in 7 healthy subjects [3]; and B) a euglycemic clamp with one or two-insulin levels in 393 non-diabetic subjects with sampling at steady state [4]. A circulatory model [5] of insulin kinetics was developed including heart and lungs, gut, liver, and extra-hepatic organs lumped together. Extra-hepatic insulin clearance was assumed constant, while saturation in the liver was described using a Michaelis-Menten function [2]. In Study A, insulin secretion was separately computed by deconvolution of plasma C-peptide; in Study B it was considered constant and estimated by simultaneously fitting plasma C-peptide concentrations, using Van Cauter's model of C-peptide clearance [6]. Parameters were estimated by mixed-effect modeling using Monolix 4.2.2.

Results: The model predicted insulin concentration adequately in both studies. The median hepatic extraction ratio was 0.57 in basal conditions, 0.25 under stimulated insulin secretion (~500 pmol/min/m^2) and 0.23 under exogenous insulin infusion (960 pmol/min/m^2). Endogenous and peripheral insulin clearance and their dependence from insulin levels were consistent with literature data [2]. Due to hepatic saturation, doubling basal insulin secretion resulted in a threefold increase in peripheral insulin concentration, a remarkable effect.

Conclusions: A new mechanistic model describing insulin kinetics in non-diabetic subjects under both basal and stimulated physiological conditions and exogenous insulin infusion has been developed. Prediction of the effects of drugs enhancing insulin secretion or of subcutaneous insulin infusion may benefit from the use of this new model in the glucose homeostasis representation.

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Janna Duong III-58 Linking mechanism-based modelling of type 2 diabetes mellitus with cardiovascular endpoints

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Objectives: Type 2 diabetes mellitus (T2DM) is by insulin resistance and deficient insulin secretion by pancreatic beta cells. Antidiabetic medications are used to restore glucose-insulin homeostasis, but it is unknown whether these medications alter i)the disease progression, and ii)therapeutic outcome (cardiovascular morbidity and mortality). A number of semi-mechanistic models has been proposed to describe disease progression in T2DM, in terms of the change in insulin sensitivity (also in relation to weight change) and the loss of beta cell function with disease progression [1,2]. In theory, these models constitute a scientific basis to differentiate between the symptomatic and the disease modifying effects of antidiabetic medications. These models have been developed solely based on the analysis of data from clinical trials and has not led to firm conclusions with regard to the eventual disease modifying effects of antidiabetic medications. Moreover, these models have not been applied to data from the real life population. Consequently, the effect on therapeutic outcome, in terms of cardiovascular morbidity and mortality, is unknown. The objective of this research is to mechanistically investigate the association between the use of anti-diabetic medications, their effects on glucose-insulin homeostasis and ultimately cardiovascular outcomes in the real-life situation.

Methods & Results: Firstly, an overview of the available glucose-insulin homeostasis and T2DM disease progression models will be prepared to select the most optimal model. Secondly, the effect of treatment on glucose-insulin dynamics will be explored in the clinical trial population using data from drug-naïve patients receiving antidiabetic medications (metformin, gliclazide, pioglitazone). The third step will be the application of this model to longitudinal data from the real life population, the Rotterdam Study [3]. Additionally, using a case-controlled study design, a preliminary analysis on the association of various covariates (including also sex, age, creatinine clearance, total cholesterol/HDL ratio and systolic blood pressure) with the risk of developing cardiovascular morbidity and mortality (incident myocardial infarction) will be performed in subjects treated either with metformin, sulphonylureas and insulin.

Conclusions: The ultimate goal is the interfacing of the mechanism-based disease progression model with the epidemiological model to assess the effect of drug treatment on the therapeutic outcome in the real life population.

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Thomas Eissing III-59 Target validation and lead optimization in drug development for diabetes using a physiologically-based PK/PD model of the glucose-insulin regulatory system

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Objectives: Realistic in-silico models of the glucose metabolism are valuable tools in diabetes research, drug development and development of treatment strategies. Existing models [1, 2] provide a good basis, but do not yet provide detail at molecular and organ level to drive fundamental research in diabetes as well as to address specific questions in drug development. We here present a framework to close this gap and specifically applied it to investigate organ-selectivity and binding properties of insulin-derivatives.

Methods: We developed a coupled physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) model of glucose metabolism [3], which provides mechanistic detail on multiple scales from whole-body level down to tissue specific insulin receptor dynamics and subcutaneous insulin absorption. The model was parameterized using literature, e.g. [4], and in-house data and has been used within clinical glucose-control trials. The variability in insulin action on a molecular level was analyzed in-silico w.r.t. molecular (i.e. receptor binding) properties of insulin analogs and organ selectivity and quantified to assess the hypoglycemia risk profile.

Results: Using this model framework the PK and PD profile of new “virtual” short-acting insulin analogues with different insulin receptor binding kinetics have been evaluated. Following a subcutaneous injection of an insulin analogue, the time profile of blood insulin plasma levels, the phosphorylation of the insulin receptor, peripheral glucose uptake, the net hepatic glucose exchange and the resulting effect on blood plasma glucose levels have been simulated and analyzed. The simulation studies provide detailed and mechanistic insights how changes of the receptor binding kinetics affect the PK and PD profile and support to shape the target product profile of new short-acting insulin analogues.

Conclusions: The modeling framework allows generating virtual diabetic populations or individualized models to support pharma diabetes R&D in defining a target product profile and in assisting lead optimization of new insulin analogues. The simulation studies in virtual patients provided novel insight, highlighted optimization potential, and supported decision making during the drug development of new insulin analogues. Overall, the diabetes PBPK/PD model provides a powerful tool to the pharmaceutical industry as decision support during the evaluation and development of novel diabetes targets, drugs, and treatment strategies on the basis of virtual diabetes populations.

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Siti Maisharah Sheikh Ghadzi IV-08 Are insulin measurements needed in glucose provocation studies? : Comparison of study power using Monte-Carlo Mapped Power (MCMP) method

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Objectives: Most glucose provocation studies are performed according to standard protocols, but the needs for insulin measurements have been questioned when performing the provocation with the aim to identify drug effects. In light of this, we performed a simulation study comparing the difference of study power between the uses of glucose plus insulin as opposed to only glucose in identifying hypothetical drug effects using model-based analysis and Monte Carlo Mapped Power (MCMP) method.

Methods: The design of the simulation study was a cross-over meal tolerance test (MTT) with two occasions and 500 subjects. Drug, 50 mg, was administered at time 0 of the second occasion and glucose, 75000 mg was administered at time 30 minutes on both occasions. Blood samples were taken at time 0 until 240-minute with 30 minutes interval. Complete datasets, including glucose and insulin, were simulated for the MCMP method using the Integrated Glucose-Insulin Meal Tolerance Test (IGI-MTT) Model with drug effects. The full dataset as well as datasets only including glucose were analysed using the IGI-MTT model with and without drug effects to assess power to detect drug effect. Six types of Emax shaped drug effects were investigated; drug effect on incretin activity, basal insulin secretion, insulin-independent glucose clearance, insulin-dependent glucose clearance, glucose production, and glucose absorption.

Results: The power to detect drug effects with a model-based approach was high for the tested magnitude of drug effects. The study power at 80% was higher with the use of both glucose plus insulin versus only glucose for all sites of drug actions, except insulin-independent glucose clearance. The largest difference in power between using insulin observation and not using insulin observation was seen in drug effect of basal insulin, followed by incretin activity and glucose absorption. No difference at 80% of study power detected for drug effect on insulin-independent glucose clearance. This indicated the need of insulin measurement in glucose provocation study, being dependent on the site of drug's action.

Conclusions: The impact on power of not measuring insulin after an MTT will depend on site of action for the drug effect.

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Fran Stringer IV-18 Evaluating the clinical influence of UGT2B15 genotype on the pharmacodynamic response of the PPAR agonist, sipoglitazar

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Objectives: Sipoglitazar, a pan-PPAR agonist was targeted for treating type 2 diabetes (T2D). Sipoglitazar undergoes conjugation catalyzed by UGT.[1] UGT2B15 genotype is a covariate for clearance in individual patients as reported previously from a PK analysis.[2] The objectives of this analysis were to evaluate the role of UGT (UGT2B15*1/*1, UGT2B15*1/*2, and UGT2B15*2/*2) driven exposure differences on the pharmacodynamic response for sipoglitazar in both FPG and HbA1c.

Methods: Efficacy of sipoglitazar was assessed in T2D patients in 2 Phase II studies (sipoglitazar QD: 8, 16, 32, 64 mg; BID: 16 or 32 mg, placebo or rosiglitazone 8mg). FPG and HbA1c samples were collected throughout (-1, 0, 2, 4, 6, 8, 10 and 12 weeks). Changes in FPG and HbA1c levels over time were described as a function of individual drug exposure using a simultaneous, cascading indirect response model structure.[3]

Results: The effects on FPG and HbA1c could successfully be described for placebo, rosiglitazone and sipoglitazar treated groups in all three UGT2B15 genotypes.[4] The Emax for sipoglitazar was estimated at 49% and AUC_{50} was 1.2 mg.day/L. Rosiglitzone treatment effect was estimated at 28% for the studied dose level.

The simulated mean change from baseline in FPG at 6 months for 64mg sipoglitazar was -1.2 mmol/L, -1.6 mmol/L and -2.1 mmol/L for UGT2B15*1/*1, UGT2B15*1/*2 and UGT2B15*2/*2 genotypes respectively (rosiglitazone 8mg, -2.0 mmol/L).

A simulation study was performed evaluating genotype-based dosing vs. single treatment approach. Using a single treatment approach, a comparable result to rosiglitazone was achieved in all genotype groups at a dose of 96mg. However for genotyped-based dose assignment a comparable result was achieved with lower doses for UGT2B15*1/*2 and UGT2B15*2/*2 groups.

FPG time profiles for genotyped and titration-based dosing were simulated. Genotype-based dosing can achieve glycemic control in a shorter duration. The difference in time to 90% of FPG steady state between genotyped and titration-based dosing was approx. 1-2 months. However, the magnitude of FPG reduction achieved for the 2 approaches would be expected to be the same.

Conclusions: In summary the genotype effect on the PK of the drug does translate to differences in FPG and HbA1c response. The application of genotyped-based dosing could be utilized to normalize clinical response between individuals. However when comparing genotyped-based dosing with a titration approach, the magnitude of response would be comparable with only a 1-2 month difference in reaching the maximum effect.

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Floris Fauchet I-05 Impact of maternal zidovudine infusions at labor on fetus: a population pharmacokinetic study

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Objectives: The aims of this study were to describe the maternal and fetal zidovudine (ZDV) pharmacokinetics resulting from the maternal administration during pregnancy (orally) and labor (infusions), to estimate the placental transfer during pregnancy and to simulate different ZDV protocols during labor in order to get the lowest percentage of fetuses with high-risk toxicity (ZDV exposure higher than 8.4 mg.h/L)[1]

Methods: In a large HIV-infected population, 74 women in active labor, 56 pregnant (PW) and 89 non-pregnant women (NPW) were included. A total of 273 maternal and 79 cord blood ZDV concentrations were collected. Women (PW+NPW) received ZDV orally twice daily. At start of labor, 2 mg/kg/h was infused during the first hour then the rate was decreased to 1mg/kg/h until delivery. The data were analyzed using the nonlinear mixed-effect modeling software NONMEM.

Results: Women plasma ZDV concentration-time courses were best described by a one-compartment model with first-order absorption and elimination. An effect compartment with two exchange rate constants represented satisfactorily the cord blood concentrations. Residual variabilities were best described by proportional error models and BSVs were estimated for CL and V. No covariates (pregnancy, maternal bodyweight, maternal age, gestational age) had significant effect on CL or V. The mean population parameter estimates (between-subject variability) were: 56 % for bioavailability, 131 liters.h^{-1} (0.358) for clearance; 188 liters (0.363) for volume of distribution, and the two exchange rate constants, 1.21 and 0.943 h^{-1}, respectively.

The placental transfer defined as fetal-to-maternal exposure ratio during pregnancy was estimated at 128 %. The median fetal exposure and the percentage of children with high-risk toxicity were 3.20 mg.h/L and 0 % after maternal oral administration; 9.71 mg.h/L and 51 % after maternal infusion during labor. Two options were considered to reduce fetal exposure during labor: (i) maternal infusion rates could be 1 mg/h/kg during 1 hour followed by 0.5 mg/h/kg, (ii) mother could only take oral ZDV every 5 hours from start of labor until delivery with her neonate having his first ZDV dose as soon as possible after birth.

Conclusions: Zidovudine exposures are very important during labor and during the first days of neonate's life[2]. Maternal ZDV dose should be decreased in labor in order to protect the fetus against risk of ZDV toxicity.

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Aline Fuchs I-08 Impact of medication adherence measurement on antiretroviral drug pharmacokinetics: A retrospective cohort study in HIV patients followed by therapeutic drug monitoring and taking part in a medication-adherence enhancing program

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Objectives: To evaluate the impact of adherence measurement on efavirenz (EFV) and lopinavir (LPV) pharmacokinetic parameters estimation and to investigate whether real dosing history as measured by electronic monitoring (EM) compared to patient self-reported last dose intake modify the interpretation of concentrations measured within the frame of therapeutic drug monitoring (TDM) program.

Methods: All adherence and pharmacokinetic data from HIV-positive outpatients followed at the medication adherence enhancing program combining EM, pill count and motivational interviews [1], with at least one LPV or EFV concentration were analysed. Population pharmacokinetic modeling was performed based on previously published studies with NONMEM® [2, 3] using both dosing time recording methods (EM and self-report). Differences in predicted individual clearance (CL) were evaluated using a paired t-test and Bland-Altman plot. Bias and precision characterizing predictive performance between the two approaches were estimated by MPE and RMSE [4].

Results: 108 EFV levels from 55 patients and 131 LPV levels from 65 patients were collected. For both drugs, population estimates of CL were similar between EM and self-report recording methods, with a good precision on parameter, whereas the volume of distribution (Vd) differed, with a higher imprecision on parameter estimate. CL interindividual variability was similar between the two approaches. No significant difference in the estimated individual CL between the two dosing time recording methods was observed for both drugs (P=0.08 and P=0.4 respectively). The Bland-Altman plot suggested that 3 patients for EFV and 6 patients for LPV had a different estimation of individual CL according to the dosing history used. Relative predictive performance were similar for self-reported and EM program for both drugs (MPE: EFV=18 ng/mL; LPV=-52 ng/mL) but with a high imprecision for LPV (RMSE: EFV=173 ng/mL; LPV=1098 ng/mL).

Conclusions: CL was statistically insensitive to reported dosing method but Vd was more affected. These differences seem however of limited clinical importance since concentration predictions were similar between the two dosing time recording methods. Despite such results, combination of both methods may help to capture complementary aspects of patients' adherence in routine care: longitudinal monitoring of patients' actual behaviour through EM and actual quantitative dosing through TDM.

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Sandra Gil I-16 Modeling the Postantifungal Effect of Anidulafungin Against Candida

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Objectives: The importance of the use of echinocandins to treat serious invasive candidiasis is increasing. Duration of the antiinfective activity after drug clears from the site of infection is important, being dose interval selection fundamental [1]. Postantifungal effect (PAFE) is defined as the continuation of suppression of fungal growth after the drug is removed. The aim of this study was to model and characterize the PAFE of anidulafungin against *Candida* isolates from in vitro static time-kill curve experiments.

Methods: For PAFE studies, *Candida albicans* and emerging species of *Candida* cells were exposed to anidulafungin for 1 hour at concentrations ranging from 0.125 to 8 μg/mL depending of the studied species. Afterwards, cell suspensions were washed and re-suspended for drug removal. Samples were taken at each lecture time point (0, 2, 4, 6, 24, 48 hours) and Colony Forming Units per milliliter were determined. Time-kill experiments were done with the same drug concentrations. Data was modeled using NONMEM v.7.2. Diagnostic plots and precision of parameter estimates were evaluated to assess model performance [2].

Results: Time-kill and PAFE data were best fit using and adapted sigmoidal Emax model that corrected for delay in the growth of *Candida*, delay on the onset of the activity of anidulafungin, steepness of the concentration-response curve, and saturation in the number of *Candida*. Additionally, a PAFE estimator, defined as the difference in the time required for counts to increase by 1 Log10 between control and after drug removal, was assessed in the mathematical model. PAFE of anidulafungin was generally long and markedly longer for *C. albicans* than for *C. parapsilosis.*

Conclusions: The anti-*Candida* postantifungal effect of anidulafungin can be accurately described using this semi-mechanistic mathematical model. Because of the prolonged PAFE of anidulafungin against *C. albicans* isolates, less frequent dosing during therapy of those infections could be considered.

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Ron Keizer I-50 Expected effectiveness of reduced-dose efavirenz

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Objectives: To increase access to antiretroviral drugs in sub-Saharan Africa it has been proposed to use efavirenz (EFV) at a reduced dose (400 mg vs 600 mg). However, antiretroviral drugs require high patient adherence to achieve therapeutic effect and avoid viral resistance, especially if co-treated with tuberculosis (TB) drugs. Using simulations we investigated whether reduced-dose efavirenz can obtain similar treatment effectiveness as standard dose.

Methods: The PK model included effects of genotypes of CYP2B6 and N-Acetyl-transferase type 2 (NAT2), and co-medication with TB drugs.[1] To correct for the auto-inductive effects of efavirenz, we speculated that at 400 mg compared to 600 mg, CLss is 25% lower, but that the inductive effect of CYP2B6 could be increased up to 100% by TB treatment. The PK model was linked to a model describing viral dynamics.[2-4] Adherence was implemented either as a Markov model or by sampling actual MEMS-caps data from HIV-treated patients. Simulations were performed in R, with ODEs solved numerically in C++/Boost. Levels of adherence that were investigated were “100%”, “80%”, “50%” and “MEMS”. Variables recorded in the simulations were the plasma concentrations over time (PK), the % of time plasma concentration

Results: Most patients with CYP2B6 519TT genotype achieved treatment success, irrespective of dose or TB co-treatment**.** However, even at 100% adherence, in patients at highest risk of sub-therapeutic dose (519GG patients with fast NAT2, co-treated with TB), treatment success was achieved for only 45% of patients at 400 mg, vs 62% at 600 mg. With “MEMS” adherence, treatment success dropped to 33% vs 49%, respectively, which was slightly worse than at 80% adherence. Overall, patients with 519GT genotypes achieved slightly higher success rates than 519GG patients.

Conclusions: Our results indicate that reduced-dose EFV is safe only for a subgroup with CYP2B6 519TT genotype and not for the 519GG and 519GT subgroups, especially when co-treated for TB. As patients are often co-treated for TB, and HIV therapy programs in sub-Saharan Africa rarely achieve high adherence levels, there is considerable risk and possibly increased costs associated with reduced-dose EFV.

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David Khan I-51 Evaluation of Mechanism Based PKPD Model for Antibiotics

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Objectives: PKPD models based on *in vitro* time-kill curve data are increasingly used in drug development for antibacterial drugs [1]. Often new PKPD models are developed to fit each situation such as different bacteria strains, increased inocula sizes and other experimental conditions. For successful forecasts of clinical effects, predictability outside traditionally used experimental conditions is vital. The aim of the current study was to perform an extensive model evaluation of a mechanism-based PKPD model built for data on ciprofloxacin and *E. coli*. The model's predictive ability was assessed on bacterial killing following; a range of start inoculum, different isogenic strains, clinical strains, and mixed population experiments with mutant bacteria competing with wild type bacteria. Its capacity to predict the earlier identified PKPD index in mice and human studies was also evaluated.

Methods: The mechanism-based PKPD model for *E. coli* exposed to ciprofloxacin was developed with static time-kill curve data for wild type and six well characterized mutants of *E. coli* (start inocula 10^6 CFU/ml) (2). The model structure includes susceptible growing and resting non growing bacteria as well as pre-existing resistant bacteria and non-plateable bacteria. The earlier estimated model parameters were used for predictions of experiments with the same strains as in the model development. When predicting isogenic and clinical strains, the EC_{50} values were taken from the MIC-EC_{50} correlation estimated from the original strains.

Results: The model successfully predicted the lower rate and extent of bacterial killing in the experiments with high start inocula without re-estimation of model parameters. The model also predicted the time-course of bacterial killing for different isogenic strains, competition experiments and identified the earlier determined PKPD index (*f*AUC/MIC). Without re-estimation, the killing of the clinical strains were over predicted at high concentrations, however, allowing for both susceptible and resting bacteria at the start of the experiment improved the fit.

Conclusions: We have shown that an earlier developed mechanism-based PKPD model can predict experiments outside the traditional settings. This study provides an extensive framework on evaluation for mechanism based PKPD models based on *in vitro* data.

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Laure Lalande II-03 Population modelling and simulation study of the pharmacokinetics and antituberculosis pharmacodynamics of isoniazid in lungs

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Objectives: To develop a pulmonary pharmacokinetic (PK) model of isoniazid (INH) and to simulate the ability of various dosage regimens to attain published target exposure of antimicrobial efficacy against *Mycobacterium tuberculosis*.

Methods: Population analysis of plasma, epithelial lining fluid (ELF) and alveolar cell (AC) data [1,2,3] from 89 subjects who received oral INH was performed using Monolix software (SAEM algorithm). The covariate selection was performed using a stepwise procedure. Matlab was then used to perform 1000-subject simulations with different dosing regimens in fast (FA) and slow INH acetylators (SA). Individual AUC_{24}/MIC (area under the concentration-curve divided by minimal inhibitory concentration) ratios were calculated in plasma and ELF for 8 MIC values ranging from 0,016 to 2 mg/L[4]. The AUC/MIC ratios were then compared to target ratios associated with a 90% killing effect on *M. tuberculosis* in a murine (567)[5] and an *in vitro* study (707,13)[6].

Results: A 3-compartment model with first-order oral absorption and linear elimination was selected. INH acetylator status significantly influenced the drug elimination and was the only covariate included in the final model. The model displayed acceptable predictive performance with mean error (ME, in mg/L) and root mean squared error (RMSE, in mg/L) of -0,14 and 1,17; 0,76 and 3,77; -1,18 and 5,24 for population predictions in plasma, ELF and AC respectively. In the simulations, a 300mg INH dose was associated with a probability of target attainment (PTA) in plasma of 53,6% in FA and 74,1% in SA for a low MIC of 0.016 mg/L, and only 0,05% in FA and 0,2% in SA for a high MIC of 0.125 mg/L. In the ELF, the PTA was 94,9% and 97,2% for the low MIC and 54,8% and 68,1% for the high MIC in FA and SA respectively. A 600mg INH dose was associated with PTA in the two acetylator groups (FA/SA) of 83,1%/92,5% for the low MIC, and 5,3%/13,5% for the high MIC in plasma. In the ELF, those respective PTA were 94,9%/97,2% for the low MIC and 54,8%/68,1% for the high MIC. The PTA were significantly lower in FA than in SA for all those simulations (χ-2 test, $p<10^{-3}$).

Conclusions: This is the first population model describing INH PK in plasma, ELF and AC. Simulations performed indicated that INH acetylator status and *M. tuberculosis* MIC may greatly influence the ability to reach INH exposures that are optimal for bacterial killing. The adult standard dose of 300mg appears to be suboptimal, especially in FA.

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Cédric Laouenan II-04 Using pharmacokinetic and viral kinetic modeling to estimate the antiviral effectiveness of telaprevir, boceprevir and Peg-IFN during triple therapy in treatment-experienced HCV infected cirrhotic patients

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Objectives: Triple therapy combining pegylated-interferon (Peg-IFN), ribavirin (RBV) and a protease inhibitor (PI, telaprevir or boceprevir) have dramatically increased the chance to eradicate hepatitis C virus (HCV). However the efficacy of this treatment remains suboptimal in cirrhotic experienced-patients. Here we aimed to better understand the origin of this impaired response by estimating the antiviral effectiveness of each drug.

Methods: Genotype 1-patients with compensated cirrhosis, non-responders to a prior Peg-IFN/RBV therapy were enrolled in the non-randomized ANRS MODCUPIC study and received either telaprevir/Peg-IFN/RBV or boceprevir/Peg-IFN/RBV. HCV-RNA and drug concentrations of each drug were frequently assessed in the first 12 weeks of treatment and were analyzed using a pharmacokinetics/viral kinetics (PK/VK) model. Trough concentrations were fitted using a constant model (PIs) or an exponential model (Peg-IFN, RBV). We used the standard biphasic model of HCV kinetics [1] and E_{max} model was using for relationship between effectiveness and concentration of each drug. Parameters and their variability were estimated using the SAEM algorithm in MONOLIX V4.2 [2]. Corrected Wald test (permutation test) was performed to detect a difference in parameters between treatment groups [3].

Results: Fifteen patients were included (9 telaprevir, 6 boceprevir). Both PIs achieved a similar level of molar concentrations (P=0.5), but telaprevir had a significantly lower EC_{50} than boceprevir (P=0.008), leading to a larger antiviral effectiveness than boceprevir in blocking viral production (99.8% vs 99.0%, respectively, P=0.002). In all patients the antiviral effectiveness of Peg-IFN was modest (43.4%) and there was no significant contribution of RBV exposure on the total antiviral effectiveness. The second phase of viral decline, which was attributed to the loss rate of infected cells, was slow (0.19 day^{-1}) and was higher in patients that subsequently eradicated HCV (P=0.03).

Conclusion: This PK/VK model provides important insights into the understanding of the impaired response to triple therapy in hard-to treat patients. Both PIs achieved a high level of antiviral effectiveness. However the suboptimal antiviral effectiveness of Peg-IFN/RBV and the low loss of infected cells suggest that longer treatment duration might be needed in cirrhotic treatment experienced-patients and that future IFN-free regimen may be particularly beneficial to these patients.

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Iris Minichmayr II-27 Target site pharmacokinetics of doripenem in plasma and interstitial space fluid of peripheral tissues

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Objectives: Doripenem is a broad-spectrum carbapenem antibiotic indicated for the empirical therapy of serious bacterial infections. Adequate drug concentrations at the site of infection are imperative to ensure successful and safe treatment. To quantify these, the method of microdialysis has proven beneficial, particularly if infections are located in peripheral soft tissues. The present analysis sought to characterise plasma and target site pharmacokinetics of doripenem and to assess its distribution characteristics into interstitial space fluid (ISF) by population pharmacokinetic modelling.

Methods: Data originated from the first part of a study in six healthy volunteers following a single 1-h infusion of 500 mg doripenem. Rich sampling was performed over a period of eight hours in plasma (n=66) and, by means of microdialysis, in the ISF of subcutaneous adipose tissue (n=65) and muscle tissue (n=66) [1]. Model development was performed in NONMEM 7.3 (FOCE Interaction). The observed dialysate concentrations were analysed using an integrated model enabling the differentiation between pharmacological drug distribution processes and methodological microdialysis-specific aspects (e.g. retrodialysis as the method of in vivo calibration) [2,3].

Results: A two-compartment disposition model with linear elimination was best suited to describe doripenem pharmacokinetics (V=26.6 L, CL=22.3 L/h). Penetration into peripheral tissues was found to be rapid and more pronounced into the ISF of subcutaneous adipose tissue than of muscle tissue. Despite the homogeneity of the population, considerable interindividual variability was observed, especially in clearance.

Conclusions: A combined population model for doripenem concentrations measured in plasma and ISF of skeletal muscle and subcutaneous adipose tissue was successfully developed. The established model will form the basis for simulating and evaluating target site pharmacokinetics for different administration schedules advocated for doripenem (e.g. prolonged infusion, continuous infusion). Furthermore, the translatability of the observed results from a healthy male population to patient populations will be investigated.

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Ingrid Ottevaere II-40 Population pharmacokinetics of ALX-0171, an inhaled Respiratory Syncytial Virus (RSV) neutralizing Nanobody.

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Objectives: The anti-RSV Nanobody ALX-0171 is developed as a nebulizer solution to enable direct treatment at the site of RSV infection. The aim of the study was to characterize the pharmacokinetics (PK) of ALX-0171 in a healthy adult population after oral inhalation or intravenous (i.v.) administration.

Methods: Population PK analyses were performed on data from 2 clinical studies, including a total of 85 healthy volunteers. Subjects were either treated i.v. or via oral inhalation with ALX-0171. Plasma concentration data obtained after i.v. administration and inhalation were modeled simultaneously. A standard bi-compartment model with first-order absorption was compared with a transit compartment model [1] or a model describing different absorption rate constants, representing the absorption process of the nebulized particles at different levels of the respiratory tract [2].

Results: PK of ALX-0171 in healthy volunteers was consistent with a bi-compartmental disposition, with first-order absorption and linear clearance from the central compartment. Implementation of transit compartments [1] or different absorption rate constants [2] did not result in a clear improvement of the goodness of fit of the inhalation data. Concentration-time profiles indicated different terminal half-lives after inhalation as compared to i.v. administration, consistent with flip-flop kinetics. The inter-individual variability in the population PK parameters was limited, and body weight and creatinine clearance were identified as covariates on absorption rate and clearance respectively.

Conclusions: The PK of the inhaled Nanobody ALX-0171, described using the standard bi-compartmental model, is consistent with prolonged lung exposure and limited systemic exposure and is in line with the expected PK properties, warranting further clinical development of inhaled ALX-0171 for treatment of RSV infection in infants.

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Gauri Rao II-52 Characterization of Oseltamivir Carboxylate (OC) Disposition using a Reduced Population (POP) Pharmacokinetic (PK) Model

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Objectives: Oseltamivir (Tamiflu) is a neuraminidase inhibitor, administered as a phosphate prodrug (OP). The non-toxic and inactive pro-drug, OP is almost completely converted to the active metabolite OC. Our aim was to develop a reduced PK model describing the disposition of OC only, from pediatrics through geriatrics.

Methods: OC plasma concentrations (conc), dosing history and demographic information was pooled from 13 clinical trials for 388 healthy and infected subjects; ages from 1 - 78 yrs and OP doses from 20 - 1,000 mg. Nonlinear mixed-effects modeling was conducted in SADAPT facilitated by SADAPT-TRANS. PK parameters were assumed to be log-normally distributed. Data below the limit of quantification was handled using Beal M3. Model discrimination was done on basis of the objective function and examination of goodness-of-fit plots. The model performance was evaluated using bootstrap analysis and VPC.

Results: The reduced PK model characterized the OC disposition reasonably well (R^2 of 0.970 for individual; 0.799 for POP fitted) compared with a full PK model [1] for OP and OC (R^2 of 0.969 for individual; 0.741 for POP fitted). The model was described by a two-compartment (CMT) model with linear clearance. Two transit CMTs accounted for the delay in conversion of OP to OC (transit rate constant, Kt), and OC was absorbed via a first order process (Ka). Residual variability was modeled using the additive plus proportional variance model. Allometric function of body weight with a fitted power function (pWt) was a significant predictor of the apparent OC clearance. Creatinine clearance was not a significant covariate. The geometric mean (%SE) parameter estimates for OC were Vc/F 19.4L (8.88), Vp/F 190L (4.47), CL/F 15.3L/h (2.31), Kt 0.631h^{-1}(2.54), Ka 1.68 h^{-1} (8.01), CL_d 53.5 (7.04), pWT 0.462(6.64).

Conclusions: The final model described OC PK well and performed as well as the full PK model. This simple model will be useful for PK/PD analysis allowing for better PK/PD parameter estimation with sparser data in future studies.

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Adedeji Majekodunmi II-60 Mixed Effect Modelling in HCV-HIV co-infected Children

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Objectives: The aim objective of this project is to investigate the effect of HCV infection on long term immune reconstitution of CD4 T cells in HIV infected children across Europe who are on anti-retroviral therapy (ART).

Methods: In a recent model developed by Lewis et al[1], it was shown that immune reconstitution in children commenced on antiretroviral therapy followed an asymptotic recovery in the first 5 yrs (zij = asyi – (asyi – inti)e-c*t + εij)[1]. However, when this model was applied to a new cohort of HIV infected children who are also coinfected with hepatitis C, a linear mixed effect model was preferentially chosen as it provided a much better fit. The data analysed was a retrospective observational data collected from 8 European paediatric HIV cohorts included in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). The children were aged btw 18 months and 25yrs and had acquired HIV/HCV infection maternally or in childhood.

Analysis was done using the principles of mixed effect modelling in R (nlme).

Results: Coinfected children appear to have higher cd4 z-scores throughout the first 5 yrs of treatment. However, this was only statistically significant in the Ukraine cohort ($p < 0.001$).

Covariate analysis revealed that age at start of antiretroviral therapy and HCV status both had significant interactions with the initial cd4 z-score (intercept) of the model ($p < 0.001$, 0.022). Age at start of antiretroviral therapy also had a significant impact on the rate of increase of cd4 z score over a 5 yr period ($p = 0.0016$). Older children have lower cd4 z-scores compared to their younger counterparts.

Conclusions: Coinfected children from Ukraine appear to have a significantly higher cd4 z-score at start of ART. This is an unexpected finding when compared with coinfected adults who are known to have lower cd4 recovery profiles[2]. A possible explanation for this could be additional homeostatic mechanisms in repopulating T cells in children. However, larger studies are needed to fully characterize immune profiles of these patients.

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Natalia Aniceto III-07 Population Pharmacokinetics-Pharmacogenetics of Efavirenz using Non-Linear Mixed Effects Modeling and Bayesian Estimation

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Objectives: Efavirenz, used in the treatment of HIV, belongs to the Non-Nucleoside Reverse Transcriptase Inhibitors class.[1] Currently, great variability is observed in the population pharmacokinetics (popPK) which hinders therapeutic management, and liver metabolism has been considered one of the main sources for this variability.[2] In order to establish the determining factors affecting popPK variability, we aim to construct a population pharmacokinetic-pharmacogenetic (PKPG) model by nonlinear mixed effects modeling (NLMEM) from sparse data, and accounting for CYP2B6 516G>T mutation (CYP2B6_SNP). Bayesian estimation of the popPK parameters was also performed.

Methods: For model construction a dataset of 15 patients with single-point high drug concentrations, demographic and biochemical data, as well as SYP2B6_SNP characterization was used. This was done using MONOLIX 4.2.2. A one compartment open model with first order absorption was used as the structural model, parameterized in terms of Clearance (CL/F) and Volume of distribution (V/F). The covariate model was built by fitting the data to each available variable and selecting the ones that improved model fitting. The selected variables were added in a stepwise manner. In parallel, Bayesian estimations of CL/F and V/F were achieved using PKS systems[3].

Results: The covariate model included CYP2B6 mutation and total bilirubin (Bil) as covariates of CL/F, both significant to the model. However no significant covariate was found for V/F. The final popPK parameters were 68.3 L ± 20, and 4.32 $L.h^{-1}$ ± 0.81 for V/F and CL/F respectively, and the covariate model for CL was: CL= -0.291*(CYP2B6_SNP)+0.971*Bil. Interindividual and residual variability in CL/F was improved in the covariate model as compared to the basic model (13% to 8%, and 26.6 to 12.6%, respectively). Good data fitting was demonstrated with the goodness of fit diagnostic plots.[4] Bayesian estimates of CL/F and V/F were 5.9 $L.h^{-1}$ ± 2.4 and 282 L ± 0.5, respectively.

Conclusions: The model was improved with Bil and CYP2B6_SNP as covariates, demonstrating the important role of this enzyme in the pharmacokinetics of Efavirenz. The covariate model partially addressed the data variability. Bayesian estimation yielded similar CL/F values to those from the NLME basic model (5.45 $L.h^{-1}$). However, V/F values from the former and the latter (96.1 L) were very different, which could stem from the high impact of initial Bayesian estimates.

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Development – Part 2: Introduction to Pharmacokinetic Modeling Methods. *CPT Pharmacometrics Syst. Pharmacol.* 2013. 2, e38.

Manel Aouri III-08 Population pharmacokinetics and pharmacogenetics analysis of Rilpivirine in HIV-1 infected individuals

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Background. Rilpivirine (RPV), the latest non nucleoside reverse transcriptase inhibitor (NNRTI) active against HIV-1, is prescribed in single pill regimen at 25 mg once a day in combination with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). The aim of this observational study was to asses RPV pharmacokinetic profile, to quantify interpatient variability and to identify potential demographic and environmental factors that could influence drug exposure in HIV positive patients.

Methods. RPV concentrations data were collected from HIV patients as part of routine therapeutic drug monitoring performed in our hospital. A population PK analysis was performed with NONMEM® by comparing various structural models and the impacts of demographic factors (body weight and age) on RPV disposition.

Results. A total of 163 plasma concentrations were measured in 141 HIV-positive patients. A one-compartment model with zero-order absorption best characterized RPV pharmacokinetics. Average RPV CL was 11.9 (L/h) (CV 20.3%), volume of distribution 285 L, and mean absorption time 4.5h. None of the recorded demographic covariates showed an influence on rilpivirine pharmacokinetics.

Conclusion. The variability in RPV pharmacokinetics appears lower than for other NNRTIs. Under the standard regimen of 25 mg per day, some patients present concentrations below the cut-off value of 50 ng/ml recently proposed as target under standard dosing regimen[1] but would remain above 12 ng/mL, an alternate target value derived from protein-adjusted in vitro data[2]**.** Further analyses are in progress to evaluate the influences of genetic polymorphisms, as well as other factors such as CYP-interfering comedications and clinical characteristics on RPV pharmacokinetics and to better characterize patients at risk of below therapeutic target exposure.

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Eduardo Asín III-09 Population Pharmacokinetics of Daptomycin in Critically Ill Patients

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Objectives: The aim of this study was to develop a population pharmacokinetic (PPK) model of daptomycin (PIP) administered to critically ill patients of the Intensive Care Unit (ICU) for the treatment of infections by *Staphylococcus aureus*.

Methods: Plasma concentration-time data were obtained from patients who received a dose of 350 or 500 mg of daptomycin every 24 or 48 hours (5.0 to 6.9 mg/kg) administered as a short intravenous infusion. Five blood samples were drawn from each patient and were analyzed using HPLC-UV. Demographic and laboratory data were collected including age, gender, body mass index, creatinine clearance, serum albumin or serum bilirrubin. The APACHE II score was reported for each patient. Total drug concentrations in plasma were modeled using NONMEM 7.2 and FOCE-I estimation method. Once a base model was selected, patient characteristics were explored for influence on PK parameters. The selected model was evaluated by bootstrap and visual predictive check.

Results: Ten patients were analyzed (3 men and 7 women) with an average age of 67 years (from 48 to 83 years) and creatinine clearance (CLCR) from 20 to 152 mL/min. A one-compartment model with first order elimination best fitted the data. Regarding the inclusion of characteristic of the patients in the model, the CLCR resulted in a significant covariate of the daptomycin total plasma clearance (CL), allowing to diminish the unexplained inter-individual variability (IIV) associated to the CL from 54.3% to 25.2%. However, none of the patient characteristics allowed to explain the IIV associated to the volume of distribution (Vd). The population Vd was 9.5 L with an associated IIV of 23.1% (shrinkage 28.8%). The daptomycin clearance was defined by the next equation: CL (L/h) = 0.131 + 0.0947·CLCR, with an IIV of 25.2% (shrinkage 4.1%). The proportional error resulted in a 30% (shrinkage 10.9%).

Conclusions: A one-compartment model best described the distribution of daptomycin in the patients. The creatinine clearance was a significant covariate of the daptomycin total body clearance, which is explained because the elimination of daptomycin is mainly renal. This model can be used to perform pharmacokinetic/pharmacodynamic analysis and optimize the dosing regimens based on the characteristics of the patients and the susceptibility of the microorganism involved in the infection.

Ana Bastos III-12 Modeling and simulation of temocillin (TMO) in patients with end stage renal disease undergoing haemodialysis

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Objectives: TMO is a narrow-spectrum anti-Gram-negative beta-lactam marketed since the '80s witnessessing renewed interest as a carbapenem-sparing drug, due to resistance to degradation by most β-lactamases.[1] TMO pharmacokinetics in hemodialysis patients has not been investigated yet. The purpose of this study was to develop a population pharmacokinetic model of TMO in patients with end stage renal disease (ESRD) undergoing haemodialysis, and to evaluate by simulation, the clinical performance of current dosing regimens.

Methods: 12 patients were administered a single dose of 1, 2, or 3g of TMO followed by a interdialytic period (off-dialysis) of 20, 44, or 68h, respectively, and a dialysis period of 4h (total of 39 administrations). 351 serum samples were collected to measure unbound concentrations using a HPLC-MS/MS assay. A population PK model was constructed and evaluated by a bootstrap analysis (internal evaluation, 1000 runs) and by comparison to an external dataset. A 1000-subject Monte Carlo simulation was conducted to determine 95% probability of target attainment (PTA_{95}) versus MIC (based on 40% time above MIC (ƒT > MIC) for measured unbound drug). Data analyses were performed using NONMEM, Pirana, PsN and R.

Results: TMO serum unbound concentrations were best described by a two-compartment model. The apparent total body TMO clearance (off-dialysis), was estimated at 1.35 L/h (bootstrap CI95% 1.084-1.966) (published value for healthy volunteers: 2.4 L/h [2]). An apparent dialysis clearance was implemented in parallel to body clearance to describe the accelerated drug clearance caused by haemodialysis (> 0 during haemodialysis; 0 during the interdialytic period). The relationship between blood flow rate and apparent TMO dialysis clearance was described using the Michaels equation [3]. TMO clearance during dialysis was 8 fold higher than off-dialysis, resulting in significant reduction of TMO serum concentration. The final model successfully predicted the serum TMO concentrations described in an haemodialysis patient unknown to the model. PTA_{95} was obtained for a MIC $\leq$ 8mg/L, for a 2g dose (44h interdialytic period).

Conclusions: A two-compartment PK model for TMO in ESRD patients undergoing haemodialysis was developed and demonstrated to be predictive, including during the dialysis period. This model might serve as a useful tool to provide guidance in the optimization of TMO dosing regimens in haemodialysis patients.

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Andrzej Bienczak III-16 Population Pharmacokinetic Analysis of Efavirenz in African Children using mixture modelling to describe clearance multimodality.

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Objectives: The aim of this project was to characterise efavirenz at steady state in African children and to evaluate the use of mixture modelling to account for multimodal clearance, as an alternative, in the absence of individual CYP2B6 genotype data.

Methods: We analysed intensive data from following studies: ARROW (n=41, age 4-12) and CHAPAS3 (n=51, age 3-13). Both studies took place at multiple sites in Uganda and Zambia and plasma concentrations of efavirenz were quantified using validated LC/MS/MS method.

Model building was conducted using NONMEM 7.2 (FOCE-I). A number of subroutines and structural models and previously published approaches were evaluated[1,2]. Model building was guided by differences in OFV, VPCs and other diagnostic plots.

Results: In total 995 sample concentrations were included in the analysis: 15% were below 1µg/ml (n=150), 29% were above 4µg/ml (n=288), and 56% were within the therapeutic range (n=577)[3].

The data was best described using a 2-compartment model with absorption through a number of transit compartments [4]. BSV was set on central and inter-compartmental clearances, and volume of central and peripheral compartments. BOV was set on bioavailability, mean transit time and absorption rate constant. Allometric scaling was used to account for effect of size[5] and typical values were estimated for an 18.5 kg child. The multimodal distribution of CL due to CYP2B6 polymorphisms was described using a mixture model. Three subpopulations were identified: extensive metabolisers (60% of the children) - 7.05 L/h, intermediate (25%) – 2.81 L/h, and slow (15%) -1.87 L/h. The model did not identify a significant effect of clearance maturation.

Conclusions: The model adequately describes the data and the mixture model significantly improved the fit. This multimodality for efavirenz clearance is consistent with previous reports, although the typical values and frequency of each subgroup found in this analysis differ from previous publications[7,8]. This may be due to the fact that in mixture modelling approach those values are estimated empirically based on the data and not on the robust information about genotype, and may be affected by other confounders. The lack of a maturation effect could be due to the fact that all children in the study were older than 3 years. In order to improve stability of the model and characterise other sources of variability incorporation of information on patients' genotype is needed.

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Jantine Brussee III-28 Modelling and simulation of the effect of L-arginine adjunctive therapy on vascular function in patients with moderately severe malaria

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Objectives: Microvascular dysfunction and the adhesion of parasitized red blood cells to the endothelium are important factors in the pathogenesis of malaria [1]. The aim of this study is to quantify the time course of the effects of adjunctive L-arginine treatment on measures of endothelial function in patients with moderately severe malaria.

Methods: Patient data has been collected for previous projects and included 73 adult patients who were suffering from moderately severe falciparum malaria [2, 3]. Thirty of these patients were included in an intervention arm and 43 in a placebo arm. Patients in the intervention arm were divided in three groups of ten different patients receiving 3 g, 6 g, or 12 g of L-arginine as a half hour infusion. A pharmacokinetic-pharmacodynamic (PKPD) model was developed to describe the time course of changes in nitric oxide (NO) concentrations and reactive hyperaemia-peripheral arterial tonometry (RH-PAT) index values. RH-PAT provides an index of endothelial function. Modelling was performed using the PPPD method [4] and the developed model was then used to explore optimal dosing regimens for L-arginine.

Results: The final PKPD model was a two-compartment PK model for arginine with endogenous production (as described by Yeo et al [3]) with two linked PD models for NO and RH-PAT. Administration of arginine resulted in immediate elevated NO concentrations and improved endothelial function in patients with moderately severe malaria. No evidence of a delay in RH-PAT was found in relation to L-arginine suggesting that constant concentrations of L-arginine may be needed to improve the duration of endothelial function. Simulations demonstrated that regimens of continuous infusion over longer time intervals could prolong the time within the therapeutic range for RH-PAT more than increasing dose amounts administered in thirty minutes.

Conclusions: In patients with moderately severe malaria adjunctive therapy with L-arginine is expected to improve endothelial function, especially within the first 24 hours of presentation when arginine and NO concentrations are significantly reduced. The optimal dosing regimen for L-arginine is likely to be administration schedule dependent. Further work is necessary to characterise the effects of continuous infusion of L-arginine on NO and microvascular reactivity in patients with severe malaria.

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Aziz Chaouch III-33 Population pharmacokinetics of oral voriconazole patients undergoing cataract surgery: modelling concentrations in plasma and in the aqueous humour

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Objectives: To model drug concentration profiles in plasma and in the aqueous humour of patients who underwent cataract surgery, following a single oral administration of 200mg voriconazole (VRC), and to assess the effect of demographic (body weight, age, gender) and phenotypic covariates (CYP2C9, CYP2C19 and CYP3A activities) on drug exposure.

Methods: Concentrations in plasma (2-3 samples per subject) and in the aqueous humour (1 sample per subject) were obtained from 33 patients (16 males, 17 females) aged 48-100y over a period of 24 hours after administration of a single oral dose of 200mg VRC. Concentration profiles were analyzed on the log-scale using a non-linear mixed-effects model (NONMEM v.7.3). The volume of distribution of the aqueous humour was fixed to 200uL according to the true physiological intracameral volume [1]. Potential influential covariates were screened using plots of Bayesian estimates of random effects versus covariates whenever shrinkage was acceptable (<30%). A stepwise forward selection procedure using a level alpha=0.05 (delta OF>3.84) was then used to incorporate covariates in the model, followed by a backward elimination procedure using a level alpha=0.01 (delta OF>6.63). Goodness of fit was assessed using standard graphical diagnostic plots as well as visual predictive checks.

Results: The data were adequately described by a 2 compartment model describing VRC in plasma and an additional compartment for characterizing concentrations in the aqueous humour with linear absorption and linear elimination. The high inter-individual variability of clearance (CV 82.1%) and volume of distribution (CV 67.9%) of the central compartment could be partly explained by covariates: clearance and central volume of distribution were influenced by body weight and fast metabolizers of CYP2C19 had higher clearances after adjusting for body weight. The coefficient of penetration of voriconazole into the aqueous humour was estimated at 50.7%.

Conclusions: VRC is characterized by an important intersubject variability that could be partially explained by body weight and CYP2C19 activity. Orally administered VRC seems to achieve therapeutic aqueous levels in the non inflamed human eye. Simulations of intraocular penetration while considering the high variability in VRC pharmacokinetics will be performed to evaluate the proportion of patients with levels above the inhibitory concentrations of most frequently encountered mycotic species involved in fungal endophtalmitis.

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Chunli Chen III-35 Population pharmacokinetic-pharmacokinetic modelling of rifampicin treatment response in a tuberculosis acute mouse model

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Objectives: To build a pharmacokinetic-pharmacodynamic (PKPD) model for rifampicin in a tuberculosis acute mice model.

Methods: Rifampicin blood concentrations after different single oral doses (1 mg/kg, 3 mg/kg, 10 mg/kg, 30 mg/kg and 100 mg/kg), single intravenous (12 mg/kg) and multiple oral administrations (10 mg/kg for 3 days) were used in the population PK analysis. One sample from each healthy mouse (n=30) after single dosing administration and several samples from each healthy mouse were available from multiple dosing administrations (n=3). C57BL/6 mice were intratracheally infected with Mycobacterium tuberculosis H37Rv at day 0. Rifampicin was administered daily by oral gavage from day 1 to day 8. At day 9, 24 hours after last administration, mice were sacrificed. Their lungs were obtained, homogenized and plated to measure the colony-forming units (CFUs) per mouse. Pharmacodynamic data [1] from mice who received multiple daily rifampicin administrations up to 8 days were include in the PD model. The PK model was first developed and thereafter the PD model was developed using a sequential fit with fixed population PK parameters. All modeling were done using NONMEM, version 7.2 [2, 3]. Xpose was used for data exploration and visualization, model diagnostics and model comparison [4]. PsN [5] was used for visual predictive check (VPC) of models.

Results: A one compartment model with first-order absorption and elimination provided the best fit to the pharmacokinetic data. The volume of distribution was significantly lower for the lowest oral dose (1 mg/kg). Inter-animal variability (IIV) in absorption rate constant (ka) and clearance (CL) was estimated to 43.8% and 18.9%, respectively. The bioavailability was estimated to 67.6%. The PD model composed by bacteria compartments, and the drug effect was introduced in the model according to the mechanism of action of rifampicin.

Conclusions: The final PKPD model described the data well and can be used for studying drug effects in mice from mono-therapy as well as drug combinations.

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Paola Coppola III-47 Pharmacokinetic assessment of prulifloxacin in patients with renal impairment using population pharmacokinetics modelling and simulations

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Objectives: Prulifloxacin (Unidrox® 600 mg tablets) is the pro-drug of ulifloxacin, a fluoroquinolone antibacterial agent.

A two-centre, open label, parallel group study has been performed to investigate the influence of renal impairment on the PK of ulifloxacin following single and repeated administration of prulifloxacin.

A POP-PK model was developed to assess the dosing regimen of prulifloxacin for renal impaired subjects.

Methods: The POP-PK model was developed using data available from 11 prulifloxacin studies. The stochastic component and covariates were introduced into the model to optimize the final PK model[1]. The POP-PK analysis was performed using NONMEM. Steady-state simulations were performed according to the validated model by reducing the dose/prolonging the frequency.

Results: The best POP-PK model was two-compartment linear model with first order absorption and elimination. Creatinine clearance (CRCL), body weight and health status significantly influenced the clearance of ulifloxacin. The final model was validated by non-parametric bootstrap and VPC[1]. Based on the model, PK profiles of ulifloxacin were simulated at steady-state in renal (mild, moderate, severe) and healthy subjects.

The results indicated that dose adjustment may be not required in mild and moderate renal subjects. In severe renal impairment a two-fold dose reduction was suggested. Preliminary PK results of the multiple dosing phase of the clinical study seem to confirm the previously simulated PK profiles.

Conclusions: Following oral administration of prulifloxacin, ulifloxacin PK is described by a two-compartment linear model with first-order absorption and elimination. The covariate CRCL described the differences in the observed ulifloxacin PK profiles. Simulations to design the dosing regimen for the renal patients suggested that no dose (600 mg QD) adjustment may be required for mild and moderate renal subjects as compared to healthy subjects. A dose reduction to 300 mg QD was instead recommended for the severe renal subjects. These dosing regimens were applied during the multiple dose phase of the renal study. The preliminary mean PK results seem to confirm the simulation predictions.

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Paolo Denti III-52 Population pharmacokinetics of cefazolin in children undergoing elective cardiac surgery

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Objectives: Cefazolin is a time-dependent antibiotic used as prophylaxis during surgical operations. For its efficacy, perioperative plasma concentrations need to be maintained above target [1]. The objective of this study is to describe the pharmacokinetics of Cefazolin in small children during cardiac surgery, characterizing in particular the effect of the cardiopulmonary bypass (CPB), with or without the use of a priming dose.

Methods: Twenty-two children undergoing cardiac surgery requiring CPB (age 1-94 months, weight 2-22 kg) were recruited in an observational study. Cefazolin 50 mg/kg was administered IV before the surgery and then every 4 to 6 hours. For 7 children, a further dose of cefazolin was added to the priming volume of the CPB circuit. Throughout the surgery, 10 to 15 blood samples were drawn from each patient, focusing on the time of sternal incision and closure, doses, and the initiation and conclusion of CPB. A nonlinear mixed-effect model was developed in NONMEM to interpret the data.

Results: A 3-compartment model with first-order elimination fit the data best. The effect of the CPB circuit during the surgery was modelled as a separate compartment, connected and disconnected from the rest of the model at the recorded times. The model correctly predicted increasing concentrations when connecting a CPB circuit primed with an extra dose, and vice-versa. The size of the CPB compartment was proportional to the priming volume. All other clearance and volume parameters were adjusted by body size using allometric scaling [2], significantly improving the fit. Clearance was found to mature, increasing with post-menstrual age [2]. The estimate of mature clearance for a 12 kg child was 1 L/h, with children born at term having 40% of this value and reaching 75% by 1 year of age. These effects explained most of the variability observed.

Conclusions: The pharmacokinetics of cefazolin in children undergoing CPB surgery was described and the main sources of variability identified in body weight and age. Although all children in the study were above the target (8 μg/mL), the model predicted the lowest concentration following the connection of a CPB not primed with extra cefazolin. The model can inform dosing strategy, strength and frequency, by adjusting for body weight and age, particularly for very small or pre-term babies.

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Konstantina Soulele IV-15 A population pharmacokinetic study of fluticasone/salmeterol in healthy subjects using two different dry powder inhalers

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Objectives: To use population pharmacokinetic modeling in order to describe the concentration-time data of fluticasone and salmeterol obtained from administration of two different dry powder inhalers: the traditional multi-dose and a novel single-dose device.

Methods: Plasma concentration – time data were obtained from a single dose 2x2 bioequivalence study comparing the two dry powder inhalers in 60 healthy male and subjects under fasting conditions. Concentration – time data of fluticasone and salmeterol were fitted to one- and two-compartment pharmacokinetic models assuming first order absorption and elimination kinetics. Elimination was considered to take place in the central compartment. Two different residual error models were tested: a proportional and an exponential error model. Demographic data like age, gender, body weight, height, and body mass index were used as covariates. The non-linear mixed effect models were applied separately to each drug (i.e. fluticasone or salmeterol) and type of inhaler. The entire work was implemented in Monolix v.4.2.

Results: For the one-compartment model, the population pharmacokinetic parameters of first-order rate constant and, the normalized with fraction of dose absorbed, volume of distribution and clearance were estimated. In case of the two-compartment model, the volume of distribution of the second compartment, as well as the first order transfer rate constants between the central and the peripheral compartment were additionally calculated. The estimates obtained from the two different dry powder inhalers were similar to each other. Significant covariates were also detected. The results found in this work were in accordance with previous studies describing the pharmacokinetics of an inhaled fluticasone multi-dose product in patients [1].

Conclusions: The utilized population pharmacokinetic models successfully described the concentration-time profile of fluticasone / salmeterol. Similar estimates were found for the two dry powder inhalers.

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Christine Staatz IV-16 A survey of intravenous tobramycin monitoring and dosage adjustment practice in cystic fibrosis patients in Australia and the United Kingdom

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Objectives: The aim of this study was to characterise current intravenous tobramycin monitoring and dosage adjustment practices in cystic fibrosis (CF) patients in Australia and the United Kingdom (UK) and compare practices between the countries.

Methods: An anonymous, online survey of health professionals caring for CF patients was conducted between November and December 2012. Survey questions were designed to obtain information on tobramycin dosing, therapeutic drug monitoring and toxicity monitoring.

Results: An online survey was sent to 232 CF health professionals. A response rate of 29.4% and 33.3% and was achieved from Australian and UK recipients respectively. Once daily dosing of tobramycin was the preferred administration regimen for 93.8% and 67.5% of CF health professionals in Australia and the UK respectively. 68.8% of Australian CF health professionals and 55% of UK health professionals initiated tobramycin therapy at a dose of 10mg/kg/day or greater. Tobramycin dosage was most commonly adjusted through calculation of tobramycin area-under-the concentration-time curve (AUC) using linear regression analysis in Australia and by use of tobramycin trough concentration measurements in the UK (See Table below).

Percentage breakdown of Dosage Adjustment Methods used across Countries

	Australia	**United Kingdom**
Linear regression analysis	40.6%	0%
Bayesian forecasting	9.4%	2.5%
Trough concentration measurement	25%	55%
Peak and trough concentration measurement	6.3%	37.5%
Nomogram	3.1%	5%
12-hour post-dose measurement	3.1%	0%
Respondent unsure	12.5%	0%

To monitor for nephrotoxicity, serum creatinine concentrations were routinely measured several times during admission by 62.5% of CF health professionals in Australia and 77.5% of CF health professionals in the UK. Ototoxicity monitoring was never routinely undertaken by 34.4% of CF health professionals in Australia and 35% of CF health professionals in the UK.

Conclusions: Health professionals in Australia are more likely to dose tobramycin once daily, use a higher initial dose of tobramycin and adjust tobramycin dosage according to an AUC estimate than those in the UK. Routine nephrotoxicity monitoring is more commonly undertaken in the UK, routine ototoxicity monitoring is not done by approximately 35% of CF health professionals in both countries.

Elodie Valade IV-33 Modified renal function in pregnancy: impact on emtricitabine pharmacokinetics

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Objectives: The aims of this study were to describe the pharmacokinetics of emtricitabine (FTC) in a large population of HIV-1-infected pregnant women and to assess the impact of pregnancy on the pharmacokinetics of this drug.

Methods: HIV-positive pregnant women, women at labor and non-pregnant women taking FTC as part of their therapeutic regimen were included. The data were analyzed using the nonlinear mixed-effect modeling software program Monolix version 4.1.3. Thanks to individual pharmacokinetic parameters, drug exposure (AUC) and minimal concentrations were obtained for each woman.

Results: A total of 457 plasma FTC concentrations from 103 non-pregnant, 46 pregnant women and 48 women at labor were available. The FTC pharmacokinetics was best described by a two-compartment model with linear absorption and elimination. The population parameter estimates (inter-patient variability) were 0.616 h-1 (0.503) for the absorption rate constant; 22.3 L/h (0.151) and 5.89 L/h for the apparent elimination and intercompartmental clearances; 100 L and 76.1 L for the apparent central and peripheral volumes of distribution. FTC apparent elimination clearance increased significantly with creatinine clearance, reflecting renal function. Median $AUC_{0\text{-}24}$ in pregnant women (8.30 mg.h/L) was significantly different from the one in non-pregnant women (9.77 mg.h/L) ($p < 0.01$). Pregnant women FTC exposures were not significantly different between trimesters of pregnancy or labor.

Conclusions: This is the first population-model describing FTC pharmacokinetics during pregnancy. Our study shows for the first time that FTC exposures differences between pregnant and non-pregnant women previously described by classical approach [1,2] can be explained by a modified renal function during pregnancy. As FTC exposure decrease during pregnancy was estimated at 15 %, dosing adjustment during pregnancy does not appear to be necessary.

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Coen van Hasselt IV-36 Development of an integrated model-based framework to support clinical development of antibiotics

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Objectives: In this project, we aim to develop a model-based framework that combines PBPK models for the prediction of target-site concentration with PK-PD models that describe the bacterial exposure-response relationships in order to predict clinical response. We will use carbapenem antibiotics (imipenem and ertapenem) as proof-of-concept compounds.

This poster describes the conceptual approach of the project and discusses potential challenges and opportunities of an integrated model-based framework that will take into account key physiological and pharmacological factors that are closely related to treatment efficacy, and which may be potentially of relevance to support the clinical development of antibiotic agents.

Methods: As first step, we aim to develop a physiologically-based pharmacokinetic (PBPK) model for ertapenem and imipenem in humans that can be applied to predict tissue-site concentrations [1] at potential infection sites. Previously reported tissue concentration-time curves for ertapenem and imipenem will be used to evaluate predictions of the developed PBPK models. Subsequently, we will develop a series of pharmacokinetic-pharmacodynamic (PK-PD) models [2] based on *in vitro* time kill experiments that describe the dynamics of antibiotic exposure-response relationships of ertapenem and imipenem for a number of clinically relevant bacterial strains.

Application: The integrated PBPK-PD framework will be used to address two key challenges in antibiotic drug development. First, we aim to evaluate the relevance of using a PBPK-PD modeling approach that takes into account local tissue concentrations and the full dynamics of antibiotic drug action, in comparison to conventional plasma-concentration based PK-PD indices. Subsequently the PBPK-PD models will be embedded in a clinical trial simulation (CTS) framework. This framework will first be applied to evaluate the predictions of clinical response according to the characteristics (trial design, patient population) of pivotal trials for ertapenem and imipenem. Thereafter, we will evaluate the CTS framework for its value to support informative clinical trial design.

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Rob van Wijk IV-39 Challenges in the evaluation of the preclinical dosing rationale for tuberculosis treatment

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Objectives: Current regimens for tuberculosis (TB) treatment have been defined empirically, making it difficult to evaluate new treatment combinations. To improve dosing decision in early drug discovery and development, an approach is proposed to determine the best ratio of current standard of care (SoC) of TB to be used in preclinical species. Given the role of drug concentration, systemic exposure, or duration of exposure above effective levels, different treatment conditions in humans will be explored and associated parameters of interest will be calculated to evaluate most suitable dosing regimens in mice.

Methods: Our analysis is based on a series of simulation analysis mimicking clinical and preclinical experimental conditions. Literature pharmacokinetic (PK) models of pyrazinamide, ethambutol, rifampicin and isoniazid [1–4] were implemented using non-linear mixed effect modelling (NONMEM). Pharmacokinetic/pharmacodynamic (PK/PD) indices AUC/MIC, t>MIC and Cmax/MIC [5] were calculated for steady state concentration profiles, based on different dosing regimens. Simulated scenarios included different ratios of antibiotics, combined with different posology (mg/kg, weight bands, and fixed dose). Variability in human pharmacokinetics was accounted for by inclusion of interindividual variability to the model parameters. Lastly, allometric scaling from the human profiles to mice was performed to assist in dosing selection in new preclinical studies.

Results: Simulated human PK profiles at the currently used dosing of SoC show surprisingly limited concentrations above MIC, as well as unfavourable AUC/MIC and Cmax/MIC ratios. The different scenarios show variation in indices values within the same population due to weight dependent dosing regimens and across subpopulations due to different absorption and elimination rates. Allometrically scaled murine concentration curves show different exposure profiles and consequently PK/PD indices values differ from the human ones.

Conclusions: An approach is developed improving dosing selection in mice, in which allometric modelling is evaluated. This shows that the currently used dosing regimens in preclinical experiments are not representative of the driving PKPD indices of the SoC. Moreover, personalised dosing regimens in humans, based on PK parameter variability are preferable, as subpopulation with different absorption or elimination should be accounted for in dosing decisions.

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Hinojal Zazo Gómez IV-52 PK/PD modelling and simulation of stavudine nanoparticles in HIV patients

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Objectives: To develop a PK/PD model to simulate, using Monte Carlo simulation, the antiviral activity of stavudine at intra-and extracellular levels, by administering stavudine nanoparticles with different schedules of administration.

Methods: The PK model describes plasma and intracellular levels of free stavudine and stavudine bond nanoparticles.The PD model based on the Hill equation predicts the inhibition of virus replication versus the stavudine concentrations[2]. This model describes the number of total CD4+T cells (Tc) and infected cells, total macrophages and infected (reservoir),and virus load in macrophages and in Tc [1]. The PK and PD parameters of stavudine were derived from the literature [3, 4].The simulation has been performed based on different modes of administration of stavudine in HIV patients: conventional tablets (Oral) (40mg / 12 hours); nanoparticles system (NP)(1mg / 12 hours by i.v.) and a combination of both (O+NP). The Monte Carlo simulations were performed to generate data of 1000 individuals during 4000 days of treatment. The software package of probabilistic simulation GoldSim Pro version 10.1 (Goldsim Technology Group, Issaquah, WA, USA) was used.

Results: Stavudine administration, by Oral regimen, achieves therapeutic steady-state plasma levels, although the intracellular levels of drug are negligible. By contrast, the administration of stavudineNP provides high intracellular levels but with very low plasma levels. The viral load–time profile shows that at the beginning of treatment most virus load is from Tc infected. Oral administration allows reducing this viral load with similar probability to O+NP. However, over the course of the disease the number of Tc decreased (around 2000 days) and the reservoir viral load began to be relevant in the total virus load. At this time, the NP lets the viral growth inhibit inside macrophages, unlike the Oral treatment. Therefore, the probability of Oral treatment efficacy is lower than O+NP treatment (probability: 30% and 70% respectively of exceeding the critical Tc value, and 20% and 7% of exceeding viral load).

Conclusions: A PK/PD model has been develop to simulate intra and extracellular stavudine concentration and their antiviral activity when administered stavudine by Oral or by NP. The administration of O+NP dosage regimens, when the number of Tc is below critical values, lets the viral load and the number of Tc control with high probability.

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Jeroen Elassaiss-Schaap I-01 Translational Pharmacokinetic/Pharmacodynamic Model of Tumor Growth Inhibition by the New Anti-PD1 Monoclonal Antibody MK-3475

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Objectives: To support dose selection of MK-3475 in the melanoma and lung cancer indications based on projection of the likely dose range associated with clinical efficacy.

Methods: MK-3475 is a monoclonal antibody targeted against the programmed-death receptor 1 and is currently under clinical development for a variety of cancers[1]. PK, receptor occupancy (RO) and tumor size data from syngeneic mice treated with an analogue of MK-3475 were used to develop an integrated PKPD model. For this, a compartmental model describing mouse PK in plasma was combined with a physiology-based tumor compartment derived from the literature [2]. The predicted concentration in tumor was linked to receptor occupancy which acted as the driver of tumor growth inhibition (TGI). The final model was translated to human by replacing the mouse PK model with a clinical PK model and system-specific parameters describing distribution and binding were substituted with the relevant human values from in vitro experiments and literature. Several different approaches of scaling the rates of tumor growth shrinkage from mouse to man were explored as scenarios in the dose-response simulations. A sensitivity analysis provided further insight into the effect of changes to parameter values on the primary response of tumor volume.

Results: Plasma PK in mice was best described by a two-compartment model with a parallel non-linear and linear clearance pathway from the central compartment. Inclusion of a feedback mechanism representing the up-regulation of PD-1-receptors in the tumor significantly improved the fit and is consistent with the mode of action of the drugThe final model adequately described the trends in the preclinical data, which was confirmed by test data not used for model development. Sensitivity analyses showed that parameters related to tumor growth, RO and receptor up-regulation were important determinants of the predicted tumor response particularly at lower doses, whereas model predictions for higher doses were less sensitive to parameter changes.

Conclusions: The translational model captured the dynamics of tumor inhibition by MK-3475, and provided important information about the biological and mathematical uncertainty in the model and the expected dose-response properties of MK-3475 in the clinic. The model was successfully applied to support the team during early development, when clinical information was still very sparse, to select a dose range for further evaluation.

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Moran Elishmereni I-02 Improved sunitinib therapy in non-small cell lung cancer as predicted by a new mixed-effects model

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Objectives: Sunitinib malate, a receptor tyrosine kinase inhibitor with multiple antitumor and anti-angiogenic properties, is an approved therapeutic agent for renal cell carcinoma (RCC), imatinib-resistant gastrointestinal stromal tumors (GIST), and pancreatic neuroendocrine tumors (NET). Despite its promising potency, sunitinib has not shown sufficient response rates in patients with non-small cell lung cancer (NSCLC). We investigated the efficacy in NSCLC, and explored alternative sunitinib regimens for this indication, by developing and simulating a semi-mechanistic mixed-effects model for sunitinib in NSCLC.

Methods: A system of ordinary differential equations describing the pharmacodynamic (PD) effects of sunitinib on tumor progression, combined with a former pharmacokinetic model for the drug [1], was designed and implemented on a Monolix platform. Data from clinical trials of sunitinib in advanced NSCLC patients post-chemotherapy, consisting of patient-specific tumor size measurements and longitudinal plasma profiles of the angiogenesis-related biomarkers, vascular endothelial growth factor (VEGF), soluble receptors for VEGF (sVEGFR2 and sVEGFR3) and KIT (sKIT), were used for fine-tuning PD model parameters. Diverse assumptions were tested, e.g. relative importance of sunitinib versus its active metabolite, delayed PD effects of the drug, development of drug resistance, etc. The model also examined the predictive significance of the soluble biomarkers in the interplay with the tumor response and the potential efficacy of altered sunitinib protocols on the patient response to treatment.

Results: Analysis of our model suggests that sunitinib has an immediate inhibitive effect on tumor growth (more than its metabolite). This effect is limited by the gradual development of resistance to the drug, a process which is reversed upon termination of therapy. The model was well fit with the tumor growth dynamics observed in the patients (R^2=0.99), and also retrieved the dynamics of the soluble receptors for VEGF and KIT. In contrast to the effects of sunitinib in GIST, the soluble biomarker parameters were not found to be inter-correlated.

Conclusions: Our results suggest that angiogenesis-related soluble biomarkers may play a less important role in lung cancer, and potentially explaining the lower efficacy of sunitinib in NSCLC.

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Sylvain Fouliard I-06 Cardiac safety monitoring in early oncology trials using optimal design and M&S approach

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Introduction: Drug-related QT interval prolongation assessment is essential in a drug development program. In the specific context of oncology, QT studies are harder to perform, and an accurate description of the PKPD relationship between drug concentration and corrected QT (QTc) may be performed by analysing electrocardiogram (ECG) data collected in early clinical trials [1]. However, the constraints of phase I/II studies induce limitations in the flexibility of administration and measurement schedules.

Objectives: This work aims at proposing a PKPD model-based ECG sampling schedule strategy for QTc prolongation detection in early clinical studies and to assess a potential effect of an anticancer drug on QTc.

Methods: First a putative PKPD model was built for study design evaluation, combining a preliminary population PK model of drug S together with a population PD model describing the circadian variation of Fridericia-corrected QTc developed using placebo data from two former QT studies and a linear drug effect on QTc, assuming these models would be predictive of the outcome of the PKPD relationship. A large range of values of the unknown drug effect on QTc was investigated as an input in optimal design software POPDES [2] in order to evaluate the ability to assess a PKPD relationship using a given study design [3]. After the completion of the study, ECG data were analysed using a sequential population PKPD approach. Model evaluation was performed through goodness-of-fit plots and NPDEs.

Results: The proposed ECG sampling design was expected to lead to a good precision of estimation of the model parameters, with expected relative standard errors (RSEs) being less than 30%. Drug S concentration-time profiles were described with a 2-compartment model with a first order absorption and first order elimination from central compartment. The circadian variation of QTc was modelled as the sum of three sine and cosine terms and drug effect was proportional to concentration. RSEs of fixed effect parameters was not higher than 30% and parameter values were close to the anticipated ones.

Conclusions: This work proposes a modelling and simulation based strategy in order to assess QTc prolongation risk in the context of clinical trials in oncology. Although the early assumptions made on PKPD relationship are not negligible and are to be confirmed, we show in this example an accurate quantification of a QTc prolongation with a feasible ECG recording design in oncology patients.

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María García-Cremades I-10 Pharmacokinetic and Pharmacodynamic analysis of Gemcitabine in pancreatic cancer in mice.

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Background: Gemcitabine is a nucleoside antimetabolite anticancer pro-drug that shows activity against several solid tumours. Its main indication given as a single agent is to treat pancreatic cancer. Gemcitabine has been chosen as model drug to build a translational approach from early (preclinical) to advanced (clinical) stages in drug development as a part of pillar 3 of working package I (models in oncology) within the IMI7 founded project, Drug Disease Models Resource (DDMoRe).

Objectives: The aim of this study is to develop a tumour growth-response model for the effects of gemcitabine in a xenograft model of pancreatic cancer. Model parameters will be used in next step to establish the translational/multi-scale model.

Methods: Information related to tumour growth was obtained from eleven studies where Gemcitabine was given i.p or p.o to athymic and CD1 nude mice (n=211) inoculated with different human derived pancreatic tumor cell lines (KP4, ASPC1, MIA PACA2, PANC1 and BXPC3). In each study, mice were randomized in two or three groups, the first one receiving saline and the rest receiving gemcitabine under different dosing schedules with dose levels varying from 15 to 200 mg/kg. Tumour volume (mm^3) was measured every three or four days. PK parameters were extracted from literature. Typical PK profiles of gemcitabine were used to describe drug response. Tumour volume versus time data were fit using the population approach with NONMEM 7.2. Model evaluation was performed through predictive checks.

Results: Different tumour growth models were tested such as the linear, exponential, and Gompertz. Models for tumour growth and corresponding parameters were found to be cell-line specific. Preliminary analysis of the data corresponding to the active treatment groups reveals that gemcitabine exerts its tumour effects reducing proliferation of tumour cells as well as promoting apoptosis. Delayed tumour shrinkage is seen with respect to time to dosing, and finally dosing schedule appear to be determinant of drug effects.

Conclusions: The modelling exercise which is currently ongoing is based on a database obtained from eleven pre-clinical studies involving a wide range of dose levels and treatment schedules. It is expected that the results from this analysis in terms of model parameters, and/or model derived descriptors can be related to metrics obtained from the outcome of clinical trials.

Ekaterina Gibiansky I-14 Population Pharmacokinetics of Obinutuzumab (GA101) in Patients with Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL)

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Objectives: Obinutuzumab (GA101) is a novel, humanized type II anti-CD20 monoclonal antibody (mAb) with a glycoengineered Fc region. The aim of the analysis was to establish a predictive population model that describes PK of GA101 following IV administration and to identify covariate factors that influence its disposition.

Methods: Serum concentrations (12,634) of 678 patients (50.4% with CLL) from 4 Phase I - III studies were analyzed in NONMEM. The full model approach was used for covariate model development. Diagnostics plots and various predictive check procedures were used for model evaluation.

Results: Consistent with other mAbs targeting B-cells, the two-compartment population PK model with time-dependent clearance ($CL=CL_{inf}+CL_T \cdot \exp(-k_{des}t)$) described GA101 concentrations. CL_T (0.23 L/day [95%CI=0.20-0.27]) was 2.8 times higher than CL_{inf} (0.083 L/day [95%CI= 0.078-0.088]). Both values (shown above for 75 kg female with CLL) depended on diagnosis. They were 17% [95%CI=11-22%] lower for B-cell lymphomas and diffuse large B-cell lymphomas, and 75% [95%CI=25-144%] higher for Mantle cell lymphomas compared to CLL. For patients with CLL and baseline tumor size (BSIZ) > 1750 mm^2, decline of time-dependent clearance ($t_{1/2}$ = 19 days) led to steady-state after approximately 4 months for 1000 mg q4w dosing (with 2 additional doses at weeks 1 and 2 of cycle 1). Clearance declined faster (higher k_{des}) for patients with NHL (by 108% [95%CI=63-164%]) and patients with BSIZ< 1750 mm^2 (by 165% [95%CI: 110-235%]). The results are consistent with target-mediated CL (with higher CL for higher tumor burden and higher CD-20 expression) that decreases with elimination of target cells.

CL_{inf} and CL_T were 22% (95%CI: 14-31%) and 49% (95%CI: 23-80%) higher in males, and increased with weight (with power coefficient (α) of 0.62 [95%CI=0.43-0.79]). Central (V_C) and peripheral (V_P) volumes (2.8 L [95%CI=2.7-2.8] and 1.0 L [95%CI=0.92-1.1]) were typical for mAbs; inter-compartment clearance (Q) was 1.3 L/day (95%CI=1.0-1.6). V_C, V_P, and Q increased with weight (with α = 0.38 [95%CI=0.29-0.47], 1, and 0.75, respectively); V_C was also 18% (95%CI=14-22%) higher in males.

GA101 PK was independent of age, renal function or anti-drug antibodies (detected in 17 subjects).

Conclusions: In CLL patients, the expected differences (<30%) in steady-state exposure based on weight and gender do not warrant a dose modification for the proposed 1000 mg IV q4w dosing regimen.

Stefanie Hennig I-29 Population pharmacokinetics of high dose methotrexate in non-Hodgkin lymphoma patients

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Objectives: Describe the population pharmacokinetics (PK) of high dose methotrexate (MTX) in patients with non-Hodgkin lymphoma (NHL) undergoing Hyper-CVAD chemotherapy protocol.

Methods: Data was collected from NHL patients who received MTX as part of the Hyper-CVAD B cycle regimen and had >1 MTX concentration measured as part of clinical drug monitoring at the Princess Alexandra Hospital during 2002–2012. The lower limit of quantification (LLQ) of the MTX assay was 0.01umol/L. Additional censoring occurred due to "dropout" from patients being discharged after 48h post-dose with MTX concentration <0.05umol/L. Censored and LLQ observations were accounted for using the maximum likelihood estimation method (M3)[1]. The population PK parameters, inter-and intra-individual variability (IIV, IOV) and the influence of covariates on the PK of MTX were estimated using NONMEM 7.2 (Laplacian). Age, body size descriptors, haemoglobin (HB), liver and renal functions were tested via step-wise covariate modelling. A decrease in the objective function value (OFV) ($X^2_{1,0.05} > 3.84$) was considered a significant improvement. Visual predictive checks and non-parametric bootstrap were used for model evaluation.

Results: A total of 847 MTX measurements from 108 adults were collected over 120 h post-dose. Patients received up to 4 cycles of MTX (1 g/m^2 over 24 h intravenously). Twelve observations were LLQ and 172 censored due to dropout. The data was best described by a 2-compartment model with a clearance (CL) of 23.3 L/h (IIV=17.1%, IOV=14.5%), inter-compartmental clearance of 2.3 L/h, volume of distribution for central (V1) and peripheral compartment of 47.7L and 26.8L, respectively with a proportional error model. Creatinine CL based on lean body weight (LBW) [2] and body size categorised by WHO criteria for underweight, normal, overweight and obese and HB on V1 reduced the OFV significantly. Explained parameter variability [3] for CL was greater than unexplained variability, suggesting clinical importance of the covariates included on CL.

Conclusions: LBW based creatinine CL and body size should be considered in optimising MTX dosing for patients receiving repeated Hyper-CVAD cycles. The influence of HB on V1 remains to be defined but may be due to fluid overload and third space accumulation.

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Mistry Hitesh I-32 Virtual Tumour Clinical: translational modelling of vemurafenib, selumetinib and docetaxel inmetastatic melanoma

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Objectives: The translation of results from animal to man is a key phase in oncology drug development. Being able to determine at which doses key biopsy measurements should be taken, or we should expect to start seeing efficacy, is important for successful evaluation of a new drug within early clinical development. Furthermore, being able to accurately translate combination schedules from mouse to man would provide significant cost savings and advance clinical development. Here we present a case study highlighting the potential applicability of Virtual Tumour Clinical in translational science.

Methods: We have developed a mathematical model of a tumour cell population called the Virtual Tumour, which has been used extensively to predict the efficacy of single drug or drug combination treatment in preclinical studies[1–4]. We have now extended and adapted our preclinical model to predict efficacy in the clinic, thereby creating the 'Virtual Tumour Clinical'.

Results: Here we show two sets of results highlighting the translational predictivity of Virtual Tumour Clinical. The first example highlights the back-translational capabilities of the model with vemurafenib; we train the model to clinical data and assess whether we can predict the outcome of xenograft studies. The second example looks at using the model for forward translation. Here we train the model to preclinical monotherapy data only for docetaxel and selumetinib, and assess whether we can predict the efficacy of both arms of a recent phase 2 trial assessing the combination versus docetaxel monotherapy[5].

Conclusions: Virtual Tumour Clinical was able to accurately back translate the effects of vemurafenib: predict xenograft changes in tumour volume using clinical data to calibrate the model. Virtual Tumour Clinical also made accurate predictions on the clinical efficacy in both arms of a phase 2 trial of docetaxel and selumetinib.

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Bart Jacobs I-37 Model based optimization of a novel controlled release formulation of capecitabine

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Introduction: Capecitabine (CAP) is an oral prodrug of 5-fluorouracil (5-FU) and is commonly used for the treatment of solid tumours. After intake, CAP is rapidly absorbed, followed by fast metabolism and clearance from the body [1]. As a consequence, there is no relevant exposure to CAP and 5-FU during approximately 6 hours of each 12-hour dosing interval. A controlled release formulation might improve CAP exposure by reducing peak levels and avoiding exposure gaps in between doses. The objective of the current study was to optimize a novel controlled release formulation of CAP with regard to tablet coating thickness using a population PK model.

Methods: Controlled release CAP tablets (500 mg) were developed by using the controlled release excipient Kollidon® SR. These tablets were coated with variable thicknesses varying from 3 - 12 mg/cm^2. Pharmacokinetics of the controlled release formulations were compared with the approved CAP formulation (Xeloda®) in a phase 0 clinical cross-over study. Patients underwent intensive pharmacokinetic (PK) sampling after administrations of Xeloda® (1000 mg) on day 1 and controlled release CAP (1000 mg) on day 2. PK data were incorporated in an earlier developed PK model for CAP, in which CAP PK from Xeloda® was described by 2-transit absorption and 2-compartmental disposition. Data analysis was performed using NONMEM, Piraña, R, Xpose and PsN.

Results: PK data from 8 patients receiving a formulation coated with 3, 6 or 9 mg/cm^2 showed controlled release and were included for analysis. A 1-transit absorption model described CAP absorption for controlled release CAP best. Increasing tablet coating thickness reduced CAP absorption rate and relative bioavailability. The effects of coating thickness on absorption rate and relative bioavailability were successfully described relatively to Xeloda® by using sigmoidal models including Hill coefficients. The effects of other coating thicknesses on CAP pharmacokinetics were simulated. Based on simulations, a coating thickness of 4 mg/cm^2 would result in CAP exposure for up to 24 h with reduced CAP plasma peak levels.

Conclusions: The absorption rate and relative bioavailability of CAP are modulated by tablet coating thickness. This study enables quick identification of formulation characteristics for *in vivo* controlled release of CAP. A tablet formulation with a coating of 4 mg/cm^2 should be considered for further clinical testing with controlled release CAP.

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Jin Jin I-41 Longitudinal Safety Modeling and Simulation for Regimen Optimization of Vismodegib in Operable Basal Cell Carcinoma

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Objectives: To determine an optimal duration of treatment interruption of vismodegib (Vismo) to minimize adverse events (AE) in patients (pts) with operable basal cell carcinoma (oBCC) using longitudinal ordered categorical models of dysgeusia/ageusia and muscle spasms, which are common AEs leading to treatment interruption/discontinuation (Tx I/D).

Methods: AE data were obtained from a phase 2 trial designed to evaluate the efficacy and safety of short-term Vismo treatment in pts with nodular oBCC. In total, 74 pts were randomized to one of three cohorts receiving 150mg QD Vismo: 12 weeks (wk) dosing with 30 days (d) follow up, 12wk dosing with 24wk observation and 30d follow up, or 8wk dosing with 4wk observation followed by 8wk dosing and 30d follow up. Individual PK profiles for unbound Vismo were predicted based on a previous population PK model incorporating individual covariates and used as driving force in the following PK/AE analyses in NONMEM (Laplacian method). AE data used in the model included severity assessment by CTCAE version 4.0 of dysgeusia, ageusia and muscle spasm. Preferred terms of dysgeusia and ageusia were grouped as they represent the medical concept of taste disturbance.

Results: AE grades in pts experiencing at least one AE were best described by a mixed-effects longitudinal logistic regression model [1] with a linear AE turn-over rate (ke0) and a linear drug effect. Saturable drug effect was also tested with no significant improvement on model fitting. The half-life of the AE turn-over rate was around 20 days for muscle spasm, and 35 days for dysgeusia/ ageusia. Vismo showed higher potency for dysgeusia/ageusia, with a potency ratio (the ratio of linear drug effect “slope”) of 1.57 relative to muscle spasm. Simulations showed that after 12wk of 150mg QD treatment, a Tx I/D of 6wk could lead to a complete resolution of muscle spasms in 80% of pts, and a Tx I/D of 4wk could lead to a significant improvement of muscle spasms without ≥Grade 2 in 95% of pts. For dysgeusia/ageusia, Tx I/D of 12wk could lead to a complete resolution of AE in 80% of pts, and Tx I/D of 6wk could lead to a significant improvement without ≥Grade 2 in 95% of pts.

Conclusions: Longitudinal safety modeling and simulation were conducted to quantitatively understand AE time profile and determine the effect of treatment interruption of Vismo in oBCC pts. Our work exemplified how longitudinal PK/PD modeling can help elucidate the onset and offset of AE events and the effect of Tx I/D, thereby enabling optimization of regimen duration.

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Victor Mangas-Sanjuan II-19 Semi-mechanistic cell cycle PKPD model of chemotherapy-induced neutropenia

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Objectives: To develop a semi-mechanistic PKPD model of neutropenia able to predict the behavior of neutrophils after different dosing schedules.

Methods: PK and PD data were obtained from five clinical studies developed at several doses and schedules involving 111 patients. Experimental data were fitted using non-linear mixed-effects modelling implemented in NONMEM 7.2[1]. Schedule 1 consisted in IV-bolus administration every 7, 14 or 21 days. Schedule 2 was represented of an oral or IV administration once daily during five days. VPC and NPC by schedule and dose level were performed as internal validation

Results: Plasma drug concentrations were fitted to a three compartment model and plasma neutrophils were modelled using five compartments, one representing proliferating cells, three representing maturation and one representing the circulating neutrophils[2]. Drug effect was described using an Emax function. Inter-individual variability of PK and PD parameters was modelled exponentially and residual variability followed a combined error model. Neutrophils from schedule 2 were simulated employing PD parameters from schedule 1. Underprediction of neutropenia levels of schedule 2 was observed in VPC performed from schedule 1 final parameter estimates. Therefore, we incorporated a cell cycle mechanism that might explain the drug acts on cells that were in a particular stage of the cell cycle.

Conclusions: Final parameters derived from schedule 1 using the model proposed by Friberg [2] were not able to capture the neutropenia observed after repeated administrations with lower doses after IV or oral administration. A modification in the model, incorporating cell cycle mechanism allowed to better predict the observations after repeated administrations.

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Ida Netterberg II-34 Predicting the absolute neutrophil count with frequent measurements during docetaxel-induced myelosuppression

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Objectives: Myelosuppression, as evaluable by absolute neutrophil count (ANC), is the dose-limiting toxicity for many chemotherapeutic agents. Today, monitoring of ANC between dosing occasions is, for practical reasons, very limited and consequences include (i) patients experiencing life-threatening conditions possible to counter-act with rescue therapy, (ii) patients returning to the oncological clinic for a new course, only to be told that their ANC is too low to start the next cycle, and (iii) cautious dosing in view of the limited possibility to monitor myelosuppression. Technological advances may make daily ANC monitoring in home-labs possible in the near future. This study aim to investigate how such data, together with model-based analysis and prediction, could improve therapy.

Methods: ANC for 601 patients administered a 1-hour infusion of 75 or 100 mg/m^2 docetaxel [1] were simulated at baseline and thereafter once daily from day 3 to 21, given the model by Friberg *et al*. [2] and parameter estimates according to the analysis by Kloft *et al*. [3]. The ANC at each day during the cycle was predicted in scenarios of varying sampling duration and frequency. Characteristics of the myelosuppression time-course, i.e. time to baseline (TBA), time to nadir (TNADIR) and ANC value at nadir (VNADIR), were computed using individual parameters estimated from simulated data and compared to the respective characteristic computed from the true individual profile. The imprecision in the predictions were expressed as root mean squared error (RMSE). Also, the ANC was forecasted in the different scenarios and evaluated as a relative estimated error (REE). The analysis was carried out using NONMEM 7.2 [4].

Results: Sampling ANC longer than approximately 15 and 12 days for TBA/TNADIR and VNADIR respectively, did not improve the imprecision. With denser sampling schedules the imprecision decreased. The RMSE of VNADIR decreased from 0.439 (805%) to 0.303 (346%) 10^9 cells/L with an ANC measurement only at baseline and data at baseline and daily from day 3 to 6, respectively. Around nadir, i.e. day 7 for docetaxel, a one day forecast of the ANC resulted in a larger bias than a one day forecast both earlier and later in the cycle.

Conclusions: Increased number of measurements of ANC together with model predictions could improve therapy with respect to patient safety, e.g. predicting nadir, and convenience for the patient and the clinic, i.e. schedule the start of the next cycle.

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Yookhwan Noh II-35 Population pharmacokinetics of HM781-36 and its metabolites in patients with advanced solid tumors

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Objectives: To develop a population pharmacokinetic (PK) model for HM781-36 and its two metabolites in patients with advanced solid tumors and determine the influence of patient demographics and baseline parameters.

Methods: Blood samples and demographic data were collected from two phase I studies in which adult patients received oral HM781-36B for various malignancies. Fifty-two patients received oral HM781-36B tablets (0.5–32 mg) once daily for 2 weeks [intermittent dosing schedule, 1 cycle for 3 weeks] and another 20 patients received oral HM781-36B tablets (12, 16, 18, 24 mg) once daily for 4 weeks [continuous dosing schedule, 1 cycle for 4 weeks]. Plasma concentration-time data of HM781-36 and HM781-36-M1/-M2 (metabolites) were analyzed with a population approach using NONMEM®.

Results: A total of 72 cases were available for analysis with no exclusions of any enrolled patients. HM781-36 PK was ascribed to a two-compartment model and HM781-36-M1/-M2 PK to one-compartment models. First, the base structural model for the HM781-36 concentration alone was constructed, and then a combined parent-metabolite PK model was made, which estimated both parent and metabolite parameters simultaneously. HM781-36 oral absorption was characterized by first-order input (absorption rate constant [KA] = 1.45 ± 0.23 h^{-1}, inter-individual variability [IIV] = 78.4%). The central volume of distribution of HM781-36 (Vc/F = 185 ± 12.7 L, IIV = 29.2%) was influenced significantly by body weight ( ). The absorption rate constant was influenced by food intake in eight patients who received HM781-36B in the fed state, and the effect was included in the final model. The typical HM781-36 apparent clearance (CL/F) was 34.5 L/h (29.4%CV), with an apparent peripheral volume of distribution (Vp/F) of 164 L (53.5%CV). The typical CLm_1/fm_1 and CLm_2/fm_2 of HM781-36-M1/-M2 metabolites were 81.7 L/h (46.9%CV) and 14.4 L/h (57.4%CV), respectively. The final PK model was validated using nonparametric bootstrapping and a visual predictive check.

Conclusions: The population PK data described here suggest that HM781-36 PKs are consistent across most solid tumor types and that the absorption process of HM781-36 is affected by the fed state before dosing. In addition, the first-pass effect was considered a significant factor influencing total bioavailability. HM781-36 PKs are not complicated by patient demographics or baseline factors, other than body weight.

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Aziz Ouerdani II-41 Tumor growth and angiogenesis mixed-effects modeling to describe the effect of pazopanib, a VEGF inhibitor, on preclinical xenograft and clinical tumor size data in renal cell carcinoma

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Objectives: To develop a mixed-effects model to describe the dynamic of tumor volume of renal cell carcinoma (RCC) xenograft in mice treated by pazopanib, an antiangiogenic compound. The model is used to leverage available tumor size data from a pazopanib phase II study and to propose new hypotheses on the mechanisms of action of the drug in patients.

Methods: 32 mice with human RCC xenografts were administered pazopanib [1] orally once daily for 24 days and tumor volume was measured twice a week (n=8 observations/mice). Longitudinal tumor size data from 47 patients with metastatic RCC treated by an oral daily dose of 800mg of pazopanib were analyzed [2]. Data were analyzed using Monolix and Nonmem. Model selection was based on the goodness of fit plots, objective function value (OFV) and BIC.

Results: The tumor growth and angiogenesis model consists of a system of nonlinear ordinary differential equations. Tumor volume (V) was described by a logistic growth dependent on carrying capacity (K) accounting for tumor angiogenesis [3]. Drug action was modeled by reducing (1) K or (2) V or (3) both (simultaneous effects on K and V). The latter model gave the best results for the pre-clinical data (ΔOFV was -67 and -47 compared to individual effect on K and V, respectively) suggesting pazopanib demonstrates both cytotoxic and antiangiogenic effects. This model, with dual mechanisms of action also was able to fit the clinical tumor size data best (BIC decrease was -72 and -23, respectively). Tumor regrowth after initial shrinkage due to the short-lived cytotoxic effect (effect on V) and subsequent decay due to the longer-lasting antiangiogenic effect (effect on K) were observed in mice after 4 and 19 days of treatment. 13% of patients have profiles consistent with the pattern of initial tumor size decrease followed by intermittent increase followed by long-term decrease. In 2 of 5 patients that dropped-out due to PD, model simulation predicts tumor shrinkage after initial growth.

Conclusions: Our model suggests that pazopanib exerts both cytotoxic and antiangiogenic effects in mice which may also occur in humans. The potential for a second decline in tumor size in a subset of patients, suggests that with this combination of mechanisms, PD may be identified prematurely in some subjects and longer treatment/follow-up may be beneficial.

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Katie Owens II-42 Population K-PD modelling of lymph node size in lymphoma patients treated with abexinostat, a histone deacetylase inhibitor (HDACi).

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Introduction: The evaluation of the Objective Response Rate (ORR) in lymphoma patients is based on the assessment of various clinical measures [1-3]. One of the clinical measures assessed for response is lymph node size, recorded as the sum of the product of diameters (SPD). The analysis of multiple types of clinical measures in an integrated framework may improve the evaluation of the ORR in lymphoma patients.

Objectives: The objective was to develop a K-PD model to characterise the time course of SPD in lymphoma patients treated with abexinostat. The overall strategy is to integrate information on lymph node shrinkage data with other clinical measures of response to optimise the prediction of the ORR in lymphoma patients.

Methods: SPD data were available for 121 patients from two phase I and II clinical studies indicated for chronic lymphocytic leukaemia (CLL) (n=19), Hodgkin's disease (HD) (n=11) and non Hodgkin lymphoma (NHL) (n=91). The patients were followed for a median time of two 3-week cycles of treatment receiving either fixed or BSA-adjusted oral doses of abexinostat under three dosing schedules. A population K-PD tumour growth inhibition (TGI) model was used to describe the SPD data, based on a longitudinal TGI model previously applied to tumour size (sum of longest diameters) and change in tumour glucose utilisation (maximal standardised uptake value) [4-5]. Dose and AUC were evaluated as predictors of change in SPD. Other clinical measures explored included PET scans, organomegaly, blood counts, circulating B lymphocyte counts, and serum monoclonal IgM concentration.

Results: The SPD data were well characterised by the TGI model. Individual fit analysis, goodness of fit plots, VPC and NPDE were used for model evaluation. 121 patients contributed to 389 SPD observations. Other categorical clinical measures investigated were PET scans, liver enlargement (n patients=114, n observations=657); spleen enlargement (n patients=113, n observations=656); continuous measures were leukocyte counts (n patients=121, n observations=2679); platelet counts (n patients=121, n observations=2660); haemaglobin concentration (n patients=121, n observations=2672); circulating B lymphocyte counts (n patients=15, n observations=67); and serum monoclonal IgM concentration (n patients=5, n observations=40).

Conclusions: The population K-PD TGI model was able to describe the time course of SPD in lymphoma patients and will be combined with other clinical measures in an integrated framework to optimise evaluation of the ORR.

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Eirini Panoilia II-43 A population PK model for bevacizumab when combined with chemotherapy in patients with metastatic colorectal cancer stage IV

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Objectives: To develop a population PK model for bevacizumab in patients with metastatic colorectal cancer (mCRC) stage IV, to evaluate the effect of VEGF polymorphisms on bevacizumab clearance (CL) and to characterize the in vivo interaction with its endogenous soluble ligand, VEGF165, so as to gain more insight into the underlying PKPD relationship.

Methods: PK and ligand data were collected from 19 adult patients with mCRC stage IV. Bevacizumab was given either at a dose of 5 and 10 mg/kg every 2 weeks, or 7.5 mg/kg every 3 weeks, by intravenous infusion together with one of the following combinations: 5-FU/Leucovorin/Irinotecan, 5-FU/Leucovorin/ Oxaliplatin, Capecitabine/Irinotecan. Bevacizumab peak and trough concentrations (86 samples) as well as pre- and post-dose VEGF165 levels (93 samples) were measured in serum by using sandwich ELISA [1,2]. VEGF polymorphisms (-2578C>A, -1154G>A, -634G>C) were identified by polymerase chain reaction (PCR) and DNA sequencing. The population PK model for bevacizumab was developed by using non-linear mixed-effects modeling implemented in NONMEM 7.3. The impact of demographic characteristics and genetics was explored on the underlying PK relationship by using a stepwise covariate model procedure (SCM). An antibody-ligand model to describe the VEGF165 profiles observed following bevacizumab administration is under development.

Results: A two-compartment model with first-order elimination best described bevacizumab concentration changes over time. The estimated CL was 0.17 L/day, the central volume of distribution (V1) was 3.1 L, the inter-compartmental clearance (Q) was 0.36 L/day and the peripheral volume (V2) was 2.6 L. An exponential distribution characterized the inter-individual variability in CL and V1 (23% and 15%) whereas the residual variability (24%) was explained by a proportional error model. Body weight was allometrically included in all PK parameters in the final model. None of the other available covariates were statistically significant. No direct relationship between VEGF polymorphisms and bevacizumab CL was identified.

Conclusions: The final population PK model adequately described the peak and trough concentrations of bevacizumab in patients with mCRC. PK parameters were consistent with those from studies on patients with solid tumors [3,4]. The antibody-ligand model is anticipated to further elucidate the role of VEGF polymorphisms in the PKPD relationship of bevacizumab.

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Zinnia Parra-Guillen II-45 Population pharmacokinetic modelling of irosustat in postmenopausal women with oestrogen-receptor positive breast cancer

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Objectives: (i) To develop a population model characterizing simultaneously the pharmacokinetic profiles of irosustat en plasma and blood after single and repeated oral administration, and (ii) to study the patient characteristics that might have a significant impact on the pharmacokinetics of irosustat.

Methods: An open label, multicentre, phase I multiple cohort dose escalation study was conducted in postmenopausal women with oestrogen-receptor positive breast cancer [1]. Thirty five patients were recruited into each of the following dose cohorts: 1 (n=3), 5 (n=7), 20 (n=6), 40 (n=13), and 80 (n=6) mg. Irosustat was administered as a single oral dose to each patient followed by an observation period of 7 days. On day 8 each patient received once daily oral administration of irosustat until day 34. Blood samples to determine the concentration of irosustat in both blood and plasma were obtained at specific times after the start of the treatment. Pharmacokinetic analyses were performed using the population approach with the software NONMEM 7.2 [2].

Results: A one compartment model with transit compartment to account for the absorption [3] process was implemented. A concentration-dependent pharmacokinetic profile was also observed and modelled considering instantaneous and reversible binding with limited distribution capacity (AMAX) of the free drug to the red blood cells (RBC).
Inter-subject variability (ISV) was supported on MTT, NN, KA, F1, kel, and a significant negative correlation was found for the ISV of KA and F1. Covariate analysis was also performed observing a significant relationship between relative biovailability and dose.
Based on the results from the model developed irosustat exhibits linear disposition properties at values of plasma concentration (C_{PL}) lower than 32.79 ng/mL and blood to plasma ratio (BPR) of 419 for the 5ng/mL dose, indicating very high affinity for the RBC compartment. Similarly, a blood clearance of 2.7 L/day was estimated, in the case of complete oral bioavailability, and under linear pharmacokinetic conditions suggesting a low clearance of the drug.

Conclusions: A non-linear population pharmacokinetic model capable to describe simultaneously the concentrations of irosustat in plasma and blood over time after single and repeated oral doses in postmenopausal women with oestrogen-receptor positive breast cancer has been developed and evaluated for a dosing range from 5 to 80 mg.

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Jonás Samuel Pérez-Blanco II-48 Population pharmacokinetic of doxorubicin and doxorubicinol in hematological patients

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Objective: To develop a population pharmacokinetic (PK) model for doxorubicin (DX) and doxorubicinol (DXol) in hematological patients.

Methods: The study has been conducted in 29 patients diagnosed of hematological malignancies and treated with 30 min intravenous infusion (25-71 mg/m^2 range doses) of DX included in different treatment schedules. From 80 plasma samples, DX and DXol concentrations were measured and fitted to a PK model using non-linear mixed-effects modeling implemented in NONMEM V7.2 (FOCEI). The analyzed covariates were: age, gender, weight, height, BSA, LBM, BMI, AST, ALT, creatinine, serum albumin, bilirubin and hemoglobin. A preliminary screening of covariates with influence on PK parameters, using GAM implemented in Xpose4 (R v.3.0.3), was conducted. S-Plus applications were used to represent the goodness of fit plot of the tested models. The stepwise covariate procedure was applied to select those ones in the final model. The evaluation of the model, using non-parametric bootstrap, was performed with the PSN program.

Results: A four compartment model, two for DX and the other two for DXol[1], both showing linear elimination, has been selected as the best structural model. The values of the distribution volumes to the different compartments were initially fixed to those proposed by Wilde et al[2]. In the final model only LBM was included on the CL_{DX} which explained a 10% of its variability[3]. The relative standard error for all fixed effect parameters was lower than 20%. Residual variabilities for DX and DXol, estimated from a proportional error model, were 15% (shr = 41%) and 42% (shr = 15%), respectively.

Gender, age, hemoglobin levels and ALT showed in the preliminary analysis some influence on the CL_{DX}, but they did not fulfill statistical criteria to be included in the final model. A larger set of data should be considered to evaluate the possible contribution of these covariates on the variability of this parameter. The proposed model showed a reasonable suitability to describe the evolution of the plasma concentrations of DX and DXol in hematological patients.

Conclusions: A suitable population PK model of DX and DXol in hematological patients has been developed. Although the model only included LBM on CL_{DX}, additional studies with a larger set of data should be performed to know if the other covariates selected in the preliminary analysis might be included in a future PK model.

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Benjamin Ribba II-55 On the use of model-based tumor size metrics to predict survival

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Objectives: Mixed-effect models are increasingly being used to analyze the time-course of tumor size and to identify tumor size metrics as predictors of overall survival in cancer patients. However, analysis of survival by tumor response may be misleading about the effect of treatment on survival [1, 2]. Our objective is to address how the use of empirical Bayes individual parameter estimates (EBE) might influence the Type 1 error of falsely detecting or failing to detect tumor size metrics as predictors of overall survival.

Methods: We simulated tumor size data by using an empirical model reported by Claret et al. [3]. Survival times were simulated independently from tumor size by sampling from an exponential distribution. The influence of using EBE on Type 1 error was explored through 9 different simulation scenarios with mean survival times from 6 to 180 weeks. The simulated tumor size data was used to obtain EBE using a mixed-effect approach (NONMEM, version 7.2). The EBE of individual parameters were used to calculate individual derived metrics: the tumor size ratio at week 6 (TSR6) and the time to tumor growth (TTG).

Results: The type 1 error was increased for TTG for all scenarios, and approached a peak of 43.4% in the scenario with a mean survival time of 48 weeks. The smaller inflation of Type 1 error observed with very short mean survival times of 6 and 12 weeks is linked to a very high shrinkage for TTG reducing the variability of the metrics across patients. The type 1 error of TSR6 was outside the prediction interval in the scenario with a mean survival time of 6 weeks. At longer survival times (36 to 180 weeks) the Type 1 error was at or below the prediction interval. When the “true” simulated individual parameters were used to calculate reference values of TTG (ITTG) and TSR6 (ITSR6), the Type 1 error rates were all within the prediction interval. These results demonstrate that the increased Type 1 error is associated with using EBE individual estimates which have high shrinkage.

Conclusions: The use of the metric TTG is problematic with substantial inflation of Type 1 error, especially, when mean survival time is close to TTG. The use of a metric similar to TSR6 as used by Wang et al. [4] could also be problematic in making appropriate drug development decisions because the Type 1 error rate is too high when the mean survival time is similar to the time of tumor size ratio evaluation and too low when mean survival times are longer.

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Dean Bottino III-21 Operating Characteristics of Tumor Kinetic Response Assessments in Early Phase Oncology Trials

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Objectives: To investigate and compare the operating characteristics of kinetic-based methods for quantifying antitumor effects of investigational anticancer agents, in particular the Change From Baseline (CFB) method and the Pre-treatment Tumor Kinetics (PTK) method which requires an additional pre-baseline tumor burden assessment [1-2].

Methods: Simulated data was generated from a (N=10^5) virtual patient population having log-normally distributed (exponential) tumor growth rates (TGRs), with median (mTGR) and %CV (cvTGR) of TGR tested over ranges encompassing clinically observed values [1,3,4]. Normalized kill rates K = (growth-kill)/growth were uniformly distributed from -1 to 1, resulting in simulated RECIST response frequencies similar to those observed in early phase oncology trials. Exponential tumor burden measurement error (8.5%) as fitted from a recent scan-to-scan variability study [5] was also simulated. For each virtual patient, the CFB estimate of K_CFB was calculated via log linear regression to assessments at -1 (baseline), 8 and 16 weeks after start of treatment. The PTK estimate K_PTK for each patient was calculated via piecewise log linear regression to assessments at -4 (pre-study), -1 (baseline), 8 and 16 weeks after start of treatment. Accuracy of each method for a given (mTGR, cvTGR) parameter set was defined as the fraction of K estimates falling within an arbitrary tolerance (+/- 0.1) of the true K values.

Results: While the PTK method was not universally more accurate than the CFB method over all (mTGR, cvTGR) parameter values tested, it was consistently more accurate than CFB over the clinically observed ranges. Specifically, PTK advantage over CFB was most pronounced in populations with fast growing tumors and highly heterogeneous TGRs, while CFB was actually more accurate than PTK in populations with very slow growing tumors and relatively homogenous TGRs. Increasing the time span between the pre-study assessment and the start of treatment from 4 weeks to 16 weeks further increased the advantage of PTK over CFB.

Conclusions: While the PTK method outperforms the CFB method in all clinically feasible scenarios tested thus far, the absolute accuracy advantage of PTK over CFB varies from negligible to significant with increasing mTGR, cvTGR, and time between pre-study baseline scans. This anticipated accuracy advantage should be weighed against the minimal additional cost of reading the pre-study scan required for the PTK method.

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Frances Brightman III-24 Predicting clinical response using preclinical data: translational modelling of docetaxel-thalidomide combination treatment in metastatic, castrate-resistant, prostate cancer

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Objectives: A major cause of drug failure is that preclinical studies do not predict with sufficient certainty what will happen in clinical practice. Accurate translation of information from animal studies to the clinic would have a major impact on attrition rate[1].

Methods: We have developed a mathematical model of a tumour cell population called the Virtual Tumour, which has been used extensively to predict the efficacy of single drug or drug combination treatment in preclinical studies[2–5]. We have now extended and adapted our preclinical model to predict efficacy in the clinic, thereby creating the 'Virtual Tumour Clinical'.

Results: Here we show a comparative study of the preclinical Virtual Tumour calibrated for prostate tumour xenografts in mice, with a Virtual Tumour Clinical version calibrated with a clinical data set comprising 53 prostate cancer patients treated with thalidomide, 25 treated with docetaxel and 50 treated with a docetaxel and thalidomide combination[6,7]. PSA measurements were used as proxy for tumour size. We analysed the consistency, the capability and the limitations of the models in translating the effect of the drug combination from the preclinical situation to the clinic.

Conclusions: Virtual Tumour Clinical was used to make successful predictions from preclinical data of docetaxel and docetaxel/thalidomide efficacy in the clinical setting.

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Claire Brillac III-26 Population PK/PD modeling of tumor growth inhibition in tumor bearing mice: a translational strategy to predict clinical efficacy ?

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Objectives: In oncology drug development, tumor growth inhibition (TGI) in xenograft mouse models are typically used to assess efficacy in preclinical setting but there is a long held debate over their clinical predictive capabilities. Therefore, a significant challenge is the selection of optimal dose and dosing regimen for the clinic. The aim of this study was to develop a translational oriented population PK/PD model of TGI for a new antibody drug conjugate (ADC), SARx, in SCID mice bearing patient-derived primary colon tumor, and then to apply a translational strategy to help selecting appropriate dosing schedule for first in human study.

Methods: First, a population PK model for SARx has been developed using data from 113 xenograft mice from a pharmacology study where SARx was administered as single i.v. bolus administration at doses of 0.75, 2.5 and 5 mg/kg. Then, a Simeoni tumor growth model was applied to tumor volume data coming from the previously described study (470 tumor volume measurements following single injection of SARx) and another efficacy pharmacology study in 42 mice evaluating single and repeated administrations from 5 to 20 mg/kg with different schedules, every 2 weeks, weekly and bi-weekly (673 tumor volume measurements). Of 1143 observations, 28.6% of tumor volumes measured were below the limit of palpation. In parallel, TK monkey data (single and multiple doses) were modelled and were used to predict SARx PK in man based on allometric scaling. The population PK and PK/PD analyses were performed using the Stochastic Approximation Expectation Maximization algorithm for nonlinear mixed-effects models implemented in MONOLIX.

Results: The TGI model was found to predict well both single and repeated dose tumor volume data. An increase of the drug potency (K2) was observed with the number of administrations when the dose is split. The typical estimated threshold concentration (CT) after repeated doses was 4.6 µg/mL. This increase in K2 is largely supported by the use of repeated dosing regimen demonstrating the interest in future clinical trial of the investigations of split administrations. The predicted PK was used to propose the minimal dose in human allowing maintaining plasma concentrations above the established CT.

Conclusions: This translational strategy may be valuable tool to help designing future clinical studies of our ADC compounds and to select the most appropriate dosing regimen for tumor eradication.

René Bruno III-27 Exposure-Response Modeling and Simulation of lucitanib Induced Dose Limiting Toxicities and Response Categories in Patients with Solid Tumors

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Objectives: Lucitanib is a multikinase inhibitor targeting FGFR1-2, VEGFR1-3 and PDGFRA/B showing a strong antitumor and antiangiogeneic activity in subcutaneous xenograft models using several human tumor cell lines. Lucitanib is undergoing a Phase I/IIa trial to determine the maximum tolerated dose and optimal dosing schedule in patients with advanced solid tumors. The drug is given 15 mg once a day (OD) with a reduction of 5 mg when dose limiting toxicities (DLT) occur. The objective of this project is to develop exposure response models for time course of graded (NCI-CTC grade) DLTs (proteinuria, asthenia) and tumor response (RECIST) as function of dosing history to simulate alternative dosing strategies that could help improving safety and efficacy.

Methods: The endpoints were analyzed independently with proportional odds ratio models. The models describe the transition probabilities of proteinuria asthenia grades and response categories as a function of dose and time. Patient dosing histories are accounted for in a virtual compartment with a first-order elimination rate driving transition probabilities. The probabilities are dependent on the preceding stage through a first-order Markov element (1-3). Multiple replications (200) of 200 patients receiving alternative dosing strategies were simulated with either continuous or intermittent dosing with various starting doses. The impact of dose reductions of 2.5 mg instead of 5 mg is also assessed. Mean delivered dose intensities across patients and days and proportion of patients with at least one grade 2 or 3 proteinuria or asthenia and responders are computed at replication level.

Results: Asthenia occurs twice faster than proteinuria (half-life of 3 vs. 6 days) and the dynamics of tumor response is slower (half-life ~9 days). Tumor response in breast cancer patients seems to be superior compared to other tumor types (p=0.004). A dose reduction of 2.5 mg would achieve slightly higher dose intensities and similar event rates than 5 mg. Scenarios with higher dose intensity are predicting better response. Drug holiday scenarios (15 mg 3 week on, 1 week off) would decrease probability of response with no clear impact on safety. Continuous administrations of 12.5 mg or 15 mg for 2 cycles followed by 10 mg would provide good performances.

Conclusions: The models compared strategies untested in the ongoing phase I/II. The results will guide the choice of the dose and administration schedule in future studies.

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Juan Pablo Cayun Pellizaris III-31 Association between genetic, adverse events and pharmacokinetics in testicular cancer patients.

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Objectives: To study the association of the genetics variants, pharmacokinetics of PEB chemotherapy and adverse events related with chemotherapy.

Methods: We recruited 63 patients with testicular cancer. Patients were treated with cisplatin, etoposide and Bleomycin (PEB). Genetics polymorphisms on *GSTM1 null, GSTT1 null, CYP3A4*1B* and *BLMH (A1450G)* were detected in these patients through PCR-RFLP [1]. A pharmacokinetics preliminary study of cisplatin was realized on 9 patients. Analysis statistical was performance with STATA 11.1 and pharmacokinetics data was analyzed with Monolix 4.2 (parametric) [2] and Pmetrics (non parametric) [3]. Association between polymorphisms and toxicity was investigated using univariate and multivariate logistic regressions and with PK parameters using Mann Whitney tests.

Results: In the univariate and multivariate analysis, we founded that *GSTM1 null patients* have a decreased risk of developing grade 3-4 leucopenia (OR=0.20, 95% IC 0.04-1.04; p=0.041), while *BLMH A/G patients* have a major risk of developing grade 3-4 leucopenia (OR=5.35, 95% IC 0.99-28.89; p=0.036) and grade 3-4 hematological toxicity (OR=57.67, 95% IC 2.14-27.35; p=0.001). A two-compartment model best described the data of cisplatin. In Monolix, the parameters values for CL and V1 were (mean ± S.D.) 7.44 ± 1.7 L/hr and 4.16 ± 3.1 L respectively and allowed a good description of the data with a bias between observed and expected concentrations of 0.236 ± 1.21. For Pmetrics, addition of an absorption phase considering a metabolic transformation (median [min-max], Ke=0.86 [0.003-3.25], V1 = 6.85 [1.2-50], Ka = 2.5 [1.4-4.9]) allowed a better description of the data with a bias between observed and expected concentrations of 0.02 ± 0.50. No association between PK parameters and genetic polymorphisms was observed using neither Monolix nor Pmetrics results.

Conclusions: Our findings show that *GSTM1 present* patients and *BLMH A/G* patients are more likely to develop grade 3-4 leucopenia. Hematological toxicity is more frequent in *BLMH A/G* patients. Nevertheless no association between PK parameters and genetic polymorphisms was shown. This is preliminary evidence in pharmacogenetics of PEB chemotherapy in testicular patients. Fondecyt Grant 1140434.

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Pascal Chanu III-32 Population pharmacokinetic/pharmacodynamic models to support dose selection of daratumumab in multiple myeloma patients

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Objectives: Daratumumab is a human CD38 monoclonal antibody with broad-spectrum antitumor activity. The aim of this project was to model the pharmacokinetics (PK), pharmacodynamic (PD) M-protein response induced by daratumumab given in patients with advanced multiple myeloma (MM) from a Phase I/II study. PK/PD modelling and simulation are used to guide dose selection of daratumumab in MM patients.

Methods: Data were available from 72 MM patients with measurable PK who received daratumumab 0.1 to 24 mg/kg at several dosing intervals (weekly to q4w) by intravenous infusion. A population PK model was developed to derive systemic exposure to daratumumab in patients. A concentration driven tumor growth inhibition model [1] was developed to describe M-protein response.

Results: A 2-compartment population PK model with parallel linear and Michaelis-Menten eliminations best described daratumumab pharmacokinetics [2]. The TGI model for M-protein confirmed a concentration dependent drug efficacy. Baseline M-Protein was found to follow a bimodal distribution. M-protein growth rate parameter was estimated similar to previous analysis [2].

Conclusions: Daratumumab was shown to inhibit tumor growth in a concentration-dependent manner in MM patients. PK/PD models are used to further optimize the dosing regimen for daratumumab and support Phase III design.

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Pieter Colin III-43 A model-based analysis of IPEC dosing of paclitaxel in rats.

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Objectives: A strong pharmacokinetic rational exists for the use of (Hyperthermic) Intraperitoneal Perioperative Chemotherapy in peritoneal carcinomatosis [1]. However, controversy remains regarding the optimal treatment strategies. Paclitaxel, a compound only seldomly used in IPEC, is believed to be a good compound for IPEC treatment because of its favourable pharmacokinetic properties [2]. Using a rat model for PC and PKPD modelling, we set out to answer some of the questions regarding IPEC treatment of PC with paclitaxel.

Methods: Rat experiments were set up to gain insight in PTX's pharmacokinetics and pharmacodynamics after IPEC treatment with Taxol®. Afterwards a Pharmacokinetic - Pharmacodynamic model was developed, that concurrently describes plasma and tumour exposure post IPEC dosing. Moreover, the developed model adequately describes the time-course of tumour apoptosis as well as the treatment effect on tumour volume.

Results: We show that the complex absorption processes underlying PTX absorption from the peritoneal cavity post IPEC dosing, give rise to a markedly non-linear dose response relationship. Furthermore, we show that, in order to optimize treatment efficiency whilst concurrently minimizing the possibility of systemic toxicities, lowering the dose and extending exposure to the cytotoxic solution is the way forward.

Conclusions: Based on the close resemblance between tumour exposure in our animal model and tumour exposure in patients treated under similar conditions, we hypothesise that, according to our findings in the rat, in the treatment of PC using IPEC administration of PTX, lowering the administered dose and prolonging the exposure time should increase treatment efficiency, whilst simultaneously keeping the risk for systemic toxicities minimal.

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Ana Margarita Contreras Sandoval III-46 PK/PD modeling of new immunotherapeutic agents in cancer

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Objectives: Immunotherapy is emerging as a new strategy in oncology to treat and cure tumors. Programmed death-1 ligand-1 (PD-L1 or B7-H1) is a co-stimulatory molecule which is expressed at high levels in tumor cells [1-4]. PD-1/PD-L1 binding interaction is able to down-regulate the immune response against tumor, inducing tolerance and enhancing tumor proliferation by inhibition of cytokines production such as interleukin (IL)-2 and interferon gamma (IFN-g) [2, 5]. According to this, PD-L1 and its receptor PD-1 at the activated lymphocytes, play a critical role in T-cell regulation to promote immune-inhibitory activity [2]. Thus, PDL-1 pathway had been proposed as a novel anti-tumor strategy, being possible to block the PD-1/PD-L1 interaction by a targeted molecule in order to increase tumor specific T-cell response [1, 2]. The development of anti-PD-L1 monoclonal antibodies (mAbs) arises as an effective approach for specific tumor immunotherapy [1], so that its pharmacokinetics and pharmacodynamics characterizations are essential.

Therefore, the aim of this work is to develop a PK-PD model able to be used as a platform for the characterization of these types of mAbs targeted to PD-L1, overexpressed on many solid tumors using a syngenic-tumor animal model.

Methods: C57BL/6 mice subcutaneously inoculated with B16F10 cells expressed ovalbumin (B16-OVA; melanoma) or MC38 (colorectal cancer) were treated with an Anti-PD-L1 mAb (clone 10F.9G2; BioXCell) at different dose schedules and/or initial tumor size. In control or saline and treated groups, tumor size and body weigh were monitored every two/three days for 50-60 days. The time profile of tumor growth will be described using a semi-mechanistic model where the impact of the schedules and the initial tumor size will also be evaluated [6]. The initial pharmacodynamics model tested to describe the control tumor growth will be based on the model previously described by Hahnfeldte et al [7].

On the other hand, additional assays are being optimized in order to quantify the anti-PD-L1 and CD8+ T cells in blood and tumor, respectively. The presence of these cytotoxic CD8 T cells is a relevant biomarker because they are required for an anticancer effective function of the immune system.

Results: The in-vivo experimentation is ongoing

Conclusions: Waiting for results

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Damien Cronier III-48 A semi-mechanistic PK/PD model of vemurafenib resistance and its rescue by LY2835219, a cyclin-dependent kinase 4/6 inhibitor, in mice bearing human melanoma xenograft tumours

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Objectives: Although vemurafenib demonstrates excellent clinical efficacy in the first-line treatment of BRAF V600E-mutated metastatic melanoma [1], resistance ultimately develops and patients relapse [2]. Experimental evidence in resistant melanoma cells indicates that MAPK pathway reactivation is a primary mechanism for resistance [3,4]; however recent studies indicate that the acquisition of resistance may also be associated with an activation of the CDK4/6 pathway through upregulation of cyclin D1 [5,6]. Consistent with these findings, CDK4/6 inhibition by LY2835219 overcomes resistance and produces tumour growth inhibition in vemurafenib-resistant A375 melanoma xenografts [6]. The objective of this study is to develop an integrated pharmacokinetic (PK)/pharmacodynamic (PD) model to characterize resistance to vemurafenib and its rescue by LY2835219 in A375 tumour xenografts.

Methods: The semi-mechanistic PK/PD model previously developed to describe cell cycle inhibition by LY2835219 [7] was extended to include vemurafenib-mediated BRAF inhibition on the MAPK pathway. Tumour shrinkage induced by vemurafenib was described by inhibition of pERK (major route) and pHH3 (minor route). A modulator compartment driving time-dependent upregulation of the MAPK pathway was incorporated to account for emerging vemurafenib resistance and increasing sensitivity to total Rb. Finally, rescue by LY2835219 was associated with LY2835219-mediated inhibition of total Rb.

Results: Vemurafenib-mediated tumour shrinkage was adequately described by the extended biomarker model. Inhibition of pERK was confirmed to be the primary contributor to tumour shrinkage, and a minor contribution of cyclin D1-mediated cell cycle arrest was identified. Resistance to vemurafenib was successfully accounted for by time-dependent over-expression of pMEK, pERK and cyclin D1. More importantly, inclusion of cyclin D1-mediated sensitivity to total Rb allowed LY2835219-mediated rescue of tumour shrinkage in resistant cells to be successfully characterised.

Conclusions: The PK/PD model successfully described the effect of LY2835219 in vemurafenib-resistant A375 melanoma xenografts. Vemurafenib anti-tumour effect and tumour resistance, followed by LY2835219-mediated rescue were described by an integrated semi-mechanistic PK/PD model. These results support the hypothesis that vemurafenib -resistant melanoma cells rely on total Rb levels for survival and support further exploration of the combination of LY2835219 and RAF inhibitors in melanoma.

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Chantal Csajka III-49 Population Pharmacokinetics of Tamoxifen and three of its metabolites in Breast Cancer patients

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Objectives: Tamoxifen (Tam) is bioactivated into active metabolites, 4-hydroxy-Tam (4OHTam) and mainly endoxifen that involves several cytochromes (CYP). Tam and metabolites present highly variable concentrations and patients with low endoxifen levels (< 6 ng/ml) are likely to achieve less benefit from their treatment. CYP2D6 polymorphism is assumed to account for active metabolites exposure variability but other CYP or co-medications may contribute as well. The aim of this analysis was to characterize the population pharmacokinetics of Tam and 3 of its metabolites and to explore the influence of genetic and non-genetic factors on their exposure.

Methods: Patients were genotyped and/or phenotyped for CYP2D6, 3A4, 2C9, 2C19 and 2B6. Plasma levels of Tam, N-desmethyl-Tam (NDTam), 4OHTam and endoxifen were measured at baseline and at 30, 90 and 120 days. A stepwise procedure with sequential addition of metabolites was used to find the best model (NONMEM®). For identifiability issues, the volume of distribution of Tam and metabolites were assumed to be equal.

Results: 507 samples were collected from 107 patients. A 4-compartment model with 1st order absorption, elimination and linear conversion to 3 metabolites described our data. Inter-individual variability was identified on Tam apparent clearance (CL/F_{Tam}: CV 30%), Tam to NDTam (k_{23}: 17%), Tam to 4OHTam (k_{24}: 29%) and NDTam to Endoxifen (k_{35}: 83%) metabolic constant rates. *CYP2D6* genotype and CYP2D6 inhibitors explained 45% of k_{35} variability. Endoxifen formation rate was reduced by 95% and 61% in CYP2D6 poor (PM) and intermediate (IM) metabolizers and by 89% and 43% in patients with potent and moderate CYP2D6 inhibitors. Impaired CYP2D6 and 2C19 activity decreased 4OHTam formation (k_{24}) by 24 and 17%, and CYP2C9 PM and IM by 30 and 13%, respectively. Proton-pump inhibitors and fluoxetine reduced k_{24} by 15 and 60%. These factors explained 33% of the variability on k_{24}. Increasing Age, CYP3A4 activity (midazolam metabolic ratio) and reported low adherence were respectively associated with a 1% decrease, 3% and 10% increase in CL/F_{Tam} and explained 16% of the variability.

Conclusion: The conversion of Tam into its active metabolites is highly variable. Pharmacogenetics and co-medication explain a significant, although not major part of this variability. Our results suggest that endoxifen therapeutic drug monitoring might be better suited for treatment optimization than the mere determination of CYP2D6 activity.

Kristin Dickschen III-53 Application of Physiologically-Based Pharmacokinetic/Pharmacodynamic Modelling in Oncology

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Objectives: Physiologically-based (PB) modelling provides a useful tool to support research and development of oncological substances, comprising both small molecules and biologics.

Methods: We developed a PB model applicable to answer oncological questions. The model includes a detailed representation of the tumor pharmacokinetics (PK) and pharmacodynamics (PD), therefore enabling a sophisticated representation of all relevant processes at the physiological level for small molecules as well as for biologics. The presented PB model for oncology was developed by use of the systems biology software suite for PBPK and PD modeling, including PK-Sim® and MoBi®. It contains a structure which enables a detailed representation of the different required modeling levels including cellular to population level. It thus can address questions arising along the drug development process from early preclinical to clinical development and species extrapolation [1-4]. Specific processes included in the model for antibody drug conjugates are on-target and off-target binding, FcRn binding as well as processes regarding target receptor availability and receptor internalization [5]. In addition, a PD model was integrated in order to be able to represent tumor growth [6]. The model was designed in a manner ready to address both; the full PK for biologics as well as for small molecules within one structure.

Results: By means of different examples it could be demonstrated that the presented PB model for oncology is well able to represent the PK and related tumor growth dynamics of small molecules as well as antibodies and antibody drug conjugates in important preclinical species.

Conclusions: The presented PB model provides useful insight into scenarios relevant for the clinical situation.

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Stefaan Rossenu IV-01 Population Pharmacokinetics of MK-3475, a human Anti-PD-1 Monoclonal Antibody in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma

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Objectives: MK-3475 is a potent antibody against the cellular immune 'switch' programmed death -1 (PD-1) with high activity in the treatment of metastatic melanoma [1]. We characterized the pharmacokinetic (PK) profile of patients receiving MK-3475 and quantified the effect of intrinsic factors on MK-3475 exposure to evaluate the need for dose modifications.

Methods: A total of 7034 serum concentrations from 337 patients were used to describe the PK of MK-3475. The relationships between all PK parameters and various baseline covariates were examined, including: age, sex, eGFR, bilirubin, AST, albumin and IgG, using stepwise covariate modeling. The posterior power of the analysis to detect clinically relevant effects was assessed using simulations in order to aid interpretation of the robustness of negative covariate findings.

Results: A two-compartmental population PK model with a linear clearance from the central compartment described well MK-3475 pharmacokinetics [2]. Clearances and volumes were allometrically scaled by bodyweight consistent with literature findings [2]. Covariate analysis identified statistically significant effects on clearance of baseline albumin (negative slope) and IgG levels (positive slope) as well as an effect of gender on clearance and central volume of distribution. Furthermore results from power simulation indicated that the power of the population PK model to detect the effect of a continuous/categorical covariate was generally 90% or higher if an effect of 20% on clearance would be present in 10% (20% for categorical covariate) of the population. The observed effects on clearance were well below effect sizes that would result in clinically relevant changes in exposure.

Conclusion: Results from this analysis indicated that PK parameters of MK-3475 have a low clearance, limited volume of distribution and low variability in the central volume of distribution (CV of 13.5%) consistent with other monoclonal antibodies [2] (CV of 26% (12-84%)). The posterior power was high allowing robust inference on the absence of impact of covariates.

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Maria Luisa Sardu IV-03 Steady-state equivalence of drug- and biomarker driven models in tumor growth experiments

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Objectives: In this work we propose a tumor growth Pharmacokinetic-Pharmacodynamic (PK-PD) modelling approach in which a tumor-specific causal biomarker [1] is integrated as driver of tumor growth in xenograft. The main goal is to investigate the mathematical properties guaranteeing steady-state equivalence of the biomarker-driven tumor growth inhibition (TGI) model to a given PK-driven TGI model.A further objective is to derive steady-state relationships between drugs and biomarker that may help predicting the drug potency in experiments involving a new drug modulating the same biomarker.

Methods: In order to characterize the steady-state behavior of a drug-driven TGI model, we evaluate the equilibrium value of the tumor weight, assuming that xenografted mice have been exposed to constant plasma concentrations of the drug, thus obtaining the so-called drug-to-tumor characteristic curve [2]. Moreover, we relate the drug potency properties of two drugs acting on the same causal biomarker. In particular, based on the steady-state equivalence between the (drug-driven) Simeoni [3] model and the proposed biomarker-driven B2-Simeoni model [2],[4], a mathematical relationship is found that allows predicting the antitumor potency of the second drug without the need of TGI data.

Results: Since the equivalence of drug- and biomarker- driven models has been considered in steady-state conditions, we resort to a simulation approach to test also the equivalence in transient conditions, using realistic model parameters. Moreover, the relationship linking drug potency on tumor growth with its effect on biomarker dynamics, is tested on data taken from the literature concerning two antitumoral drugs acting on the same biomarker [5]. The models are identified using experimental PK data, and biomarker data for the two drugs while only tumor growth data for the first compound are employed. Then model properties are used to predict both the antitumor potency of the second drug and the associated tumor growth profile.

Conclusions: In this work, starting from an established drug-driven TGI model, a biomarker-driven TGI model that is steady-state equivalent has been investigated. A relationship linking drug potency on tumor growth and drug effects on biomarker dynamics is obtained that can be used to predict the antitumoral drug potency of a new drug acting on the same path without the need of performing additional tumor growth experiments.

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Emilie Schindler IV-05 PKPD-Modeling of individual lesion maximal standardized uptake value (SUV) in Gastro-Intestinal Stromal Tumors (GIST) patients treated with sunitinib

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Objectives: Tumor glucose metabolism - determined by the maximal standardized uptake value (SUV) assessed by [18F]-fluorodeoxyglucose positron emission tomography - has been suggested as an alternative to tumor size to assess early tumor response to therapy in cases where clinical benefit is observed but a change in tumor size is limited or delayed, e.g. for cytostatic drugs [1]. This analysis aims to investigate potential relationships between sunitinib exposure and individual lesion SUV time-course and to characterize both inter-individual (IIV) and inter-lesion variability (ILV) in SUV response in gastro-intestinal stromal tumors (GIST) treated with sunitinib, a multi-targeted tyrosine kinase inhibitor.

Methods: Baseline and post-baseline SUV data (n=607) were available for 172 lesions from 66 patients followed for a median time of 10 weeks of treatment with three different oral doses of sunitinib under three different treatment schedules [2]. Indirect response (IDR) models with inhibition of the production or stimulation of the loss of response with linear, power and E_{max} drug-effect relationships were investigated to describe SUV time-course. IIV and ILV were allowed in all model parameters. ILV was implemented in NONMEM in a manner similar to inter-occasion variability. The individual lesions' SUV that had been assessed from the same FDG-PET scan were allowed to have different residual error values, but were assumed to be sampled from the same variability distribution and correlated.

Results: Log-transformed SUV data were well characterized by an IDR model with stimulation of the loss of response through a linear drug effect model driven by daily AUC. The model predicted a typical decrease in SUV of 60% after 14 days of sunitinib treatment (50 mg qd). A linear disease progression was included and predicted a typical increase in SUV of 14% per year. The estimated IIV was larger than the estimated ILV for both SUV baseline (33% CV for IIV vs 23% CV for ILV) and the drug effect parameter (59% CV for IIV vs 49%CV for ILV). The typical doubling time of SUV for return to baseline during off-treatment periods was 2 weeks.

Conclusions: Significant IIV and ILV in SUV response could be identified in the developed lesion model. VPCs illustrated the capability of the model to predict the drug effect on individual lesion SUV, as well as the sum of SUV at each time point. The predictive ability of individual lesion SUV on overall survival is under investigation.

Acknowledgements: This work was supported by the DDMoRe (www.ddmore.eu) project.

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Kwang-Hee Shin IV-10 A population pharmacokinetic/pharmacodynamic approaches of a peglyated granulocyte-colony stimulating factor (G-CSF) in healthy Korean

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Objectives: A pegylated recombinant human granulocyte colony stimulating factor (G-CSF) has been used for treatment of neutropenia in cancer therapy. The study aimed to develop a pharmacokinetic/pharmacodynamics (PK/PD) model of a pegylated G-CSF in healthy Korean to explore the relationship between plasma drug concentration and drug effect, absolute neutrophil count (ANC).

Methods: A dose-block randomized, double-blind, single-dose study was performed. Twenty five volunteers were randomly received a single subcutaneous (SC) pegylated G-CSF injection at a dose of 30 (n=10), 100 (n=10), or 300 (n=5) μg/kg or placebo in a 4:1 ratio. Plasma concentrations (PK) and ANC (PD) data were obtained up to 14 days after study drug administration. The data were fitted to a PK/PD model using non-linear mixed-effects modelling implemented in NONMEM V7.2.0 [1].

Results: Sequential PK/PD model was developed and the first-order conditional estimation with interaction in NONMEM was employed for model run. A one-compartment model with first-order absorption and first-order elimination described the PK. Stimulatory E_{max} model was well fitted for ANC profiles.

Conclusions: The time-profiles of the concentration and ANC in healthy Korean were well described by the developed model. Further PK-PD modeling with patient data may be useful tool to provide clinically relevant dosage regimen in neutropenia patients.

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Mark Stroh IV-19 Meta-analysis of Published Efficacy and Safety Data for Docetaxel in Second-Line Treatment of Patients with Advanced Non-Small-Cell Lung Cancer

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Objectives: Meta-analysis of published trial data for docetaxel monotherapy was undertaken to elucidate its efficacy and safety profile in second-line non-small-cell lung cancer (NSCLC).

Methods: A literature database was constructed based on a review of published trials including docetaxel monotherapy treatment arms. Grade 3/4 neutropenia, overall response rate (ORR), and overall survival (OS) were selected for model-based meta-analysis (MBMA). In addition to assessing dose-response relationships, effects of treatment regimen and population characteristics were examined. Neutropenia and ORR were modelled using logistic regression. For OS, Kaplan-Meier curves were modelled based on a reference survival curve and benchmark prognostic factors[1]. The reference curve was derived from a published meta-analysis of individual data from second-line NSCLC (Di Maio analysis)[2].

Results: The literature database included 46 unique trials, with 57 treatment arms and summary-level data for 6085 NSCLC patients receiving docetaxel alone as second-line therapy. Doses ranged from 25 mg/m2 to 100 mg/m2 with 1036, 158, and 4891 subjects treated with QW, Q2W, and Q3W regimens, respectively. Neutropenia, ORR, and OS data were reported for 51, 52, and 52 of the 57 treatment arms.

Grade 3/4 neutropenia incidence was described as the inverse logit of a linear function of dose (odds ratio (OR) = 1.05 per unit increase in dose, 95% CI 1.04 to 1.06), with a Japanese study effect (OR = 17.1, 95% CI 6.05 to 48.4) capturing the substantial increase in neutropenia evident in the three Japanese studies included in the database. ORR was described as the inverse logit of a linear function of actual cumulative dose (OR = 1.004 per unit increase in cumulative dose, 95% CI 1.001 to 1.008) and median population age (OR=1.08 per year, 95% CI 1.02 to 1.15). For both neutropenia and ORR, docetaxel exposure (dose or cumulative dose) was a stronger predictor than regimen (Q3W versus QW). No dose-response relationship was detected for OS; however, a Japanese study effect (HR=0.65, 95% CI 0.51 to 0.84) was quantified in addition to the prognostic factors identified by the Di Maio model.

Conclusions: MBMA revealed dose-response relationships for neutropenia and ORR, as well as important population characteristics that influence the three endpoints examined. These findings can be used to support trial design and normalize results for patient prognostic factors in support of approval of new therapies.

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Kim Stuyckens IV-21 Modelling and simulation approach to optimize the pharmacological activity during a Phase 1 study of JNJ-42756493, a selective and potent FGFR 1, 2 ,3 and 4 inhibitor.

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Objectives: JNJ-42756493, an oral potent and selective FGFR1,2,3 and 4 inhibitor, is currently under development for patients with cancer with FGFR aberrations. A pharmacokinetic/pharmacodynamics (PK/PD) model approach to support the dosing strategy was applied for managing safety by controlling serum phosphate and calcium homeostasis and safeguarding efficacy.

Methods: After each dose level of the dose escalation portion of a first in human study, biomarkers indicative of efficacy and safety, plasma PK as well as AE information were evaluated. A population PK model was developed using non-linear mixed-effects modelling (NONMEM 7.2) to assess exposure profiles across the different dose levels (0.5, 2, 4, 6, 9, 12 mg QD). JNJ-42756493 human plasma exposure profiles were projected on the window of threshold concentrations for efficacy based on a mouse xenograft PK/PD model [1]. In addition, exposure profiles were linked to mode of action-related safety and efficacy biomarkers: FGF23, serum phosphate, parathyroid hormone, calcium, and vitamin D.

Results: A two-compartment model with first-order absorption was shown to accommodate JNJ-42756493 PK data. Body weight on Vc/F and alpha-1-acid glycoprotein (AGP) on CL/F and Vc/F were identified as the most significant covariates affecting the absorption and distribution characteristics of the drug. Likely due to the variable AGP levels in patients (45-254 mg/dL) and the extensive binding to AGP, the unbound fraction ranged between individuals (0.1-0.8%), influencing the inter-patient variability of PK. PK were dose-proportional and time independent over the tested dose range. Apparent clearance and distribution volumes were relatively low; the compound had a half-life of approximately 3 days. Since hyperphosphatemia was observed at the higher doses, PK-PD models linking phosphate and exposure were developed to allow simulating various dosing strategies, thereby maintaining exposures within the xenograft based efficacy window controlling phosphate levels. Simulated dosing strategies are currently tested in the clinic.

Conclusions: Modelling and simulation of JNJ-42756493 pharmacokinetics and pharmacodynamics helped the conduct of the 1 study, safeguarding efficacy while remaining below predefined safety thresholds.

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Siddharth Sukumaran IV-22 Development of a Mechanism-based pharmacokinetic model for MMAE conjugated ADCs

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Objectives: Antibody drug conjugates (ADC) are often produced and administered as a mixture of conjugated antibodies with different drug to antibody ratios (DAR) resulting in complex heterogeneous disposition kinetics. Results from i*n-vivo* pre-clinical studies suggest that ADCs with different DAR show differential total antibody clearance. The purpose of this study is to develop a mathematical model that can describe and predict the complex PK behavior of MMAE conjugated ADCs by incorporating known mechanisms including DAR dependent antibody clearance and drug deconjugation. Pharmacokinetic disposition of ADCs in cynomolgous monkeys was used for model development.

Methods: Model development, data fitting and simulations were performed in MathWorks SimBiology software. PK data for total antibody and antibody conjugated MMAE (AcMMAE) concentrations were obtained after single intravenous administration of 0.3 mg/kg and 1 mg/kg Anti-Steap1 (or Napi2b)-Vc-MMAE (average DAR~3.5) and 1 mg/kg unconjugated Anti-Steap1 (or Napi2b) antibody in cynomolgous monkeys. Total antibody was measured by ELISA and AcMMAE by LC-MS. The structure of the mathematical model was developed based on the known mechanisms and observed impact of DAR on ADC pharmacokinetics. Specifically, models accounting for DAR dependent clearance and drug deconjugation were assessed by simultaneous fitting of different PK analytes.

Results: The model includes 10 distinct species (DAR0-8 ADC and unconjugated antibody), each represented by a two compartment model (central and peripheral) with common distribution parameters. Optimal fits were obtained, with deconjugation rates linearly dependent on DAR and proteolytic clearance increasing exponentially with DAR. The final model described PK profiles (total antibody and/or AcMMAE concentrations) of both Anti-Steap1 and Anti-Napi2b ADCs along with their unconjugated antibody counterparts in cyno. Final estimated parameters related to DAR dependent clearance and de-conjugation were comparable between Anti-Steap1 and Anti-Napi2b suggesting a common mechanism irrespective of the target.

Conclusions: The integrated PK model was developed based on the known mechanisms of ADC disposition kinetics and the model serves as a platform for describing complex PK behavior of MMAE conjugated ADCs in cynomolgous monkeys with potential translational application for human PK prediction.

Ahmed Suleiman IV-23 A survival modeling analysis evaluating the use of positron emission tomography with [(18)F]-fluorodeoxyglucose for predicting the prognosis in advanced non-small cell lung cancer patients first-treated with erlotinib

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Objectives: Positron emission tomography (PET) using [(18)F]-fluorodeoxyglucose (FDG) has been promoted over size-based assessment tools for predicting the response to novel anticancer agents with mechanisms unlikely to result in tumor shrinkage[1-3]. Several criteria to quantify the standardized uptake value (SUV) of FDG have been proposed[4], yet a consensus on which criteria to use has not been reached. Using data from a clinical study conducted in patients with advanced non-small cell lung cancer (NSCLC) first-treated with erlotinib[3], we aimed to develop a survival model describing the times-to-death distribution of the cohort, and to evaluate different factors including the tumor metabolic dynamics represented by the SUV of FDG as overall survival (OS) predictors. Using the model developed, we also aimed to compare the prognostic predictive abilities of different criteria used for SUV quantification.

Methods: Data from patients with stage-IV NSCLC (n=39) first-treated with erlotinib (150mg/day) were used[3]. Three FDG-PET scans were scheduled at baseline, 1 and 6 weeks after starting treatment. A parametric time-to-death model was developed by testing exponential, Weibull, Gompertz, and log-logistic distributions for best description of OS. FDG uptakes (quantified as SUV_{peak}, SUV_{max} and SUV_{50}; defined in [4]) measured at baseline, relative changes after 1 and 6 weeks of treatment, demographics, histology, presence of a mutation in the epidermal growth factor receptor domain, smoking and baseline performance statuses were tested as OS predictors. Non-linear mixed effects modeling using NONMEM 7.3 was used for analysis.

Results: OS was described using an exponential distribution. For all SUV definition criteria, the baseline SUV and the relative change in SUV after 1 week of treatment were consistently found as statistically significant predictors of OS ($p<0.05$). For every unit increase in FDG uptake measured at baseline as SUV_{peak}, SUV_{max} or SUV_{50}, the death hazard increased by 25%, 15% and 26%, respectively, while the hazard decreased for every 10% drop in FDG uptake quantified as SUV_{peak}, SUV_{max} or SUV_{50} after 1 week of treatment by 17%, 13% and 13%, respectively. No other tested covariates predicted OS.

Conclusions: Regardless of the criteria used for quantifying FDG uptake, FDG-PET can be used as an early survival predictor for advanced NSCLC patients treated first-line with erlotinib.

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Nadia Terranova IV-26 An energy based model able to describe the effect of anticancer drugs on tumor growth and host body weight

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Objectives: Cachexia is a complication responsible for around 20% of cancer deaths. For this reason, in preclinical pharmacological models, the decrease in the net body weight time course is considered a fundamental toxicological parameter to be evaluated. In both settings the energy loss caused by the tumor growth within the body is considered one of the causes of this side effect. Models based on dynamic energy budget (DEB) theory for describing the dynamics of the tumor host interaction are currently available; however the effect of anticancer treatments should also be considered. For this purpose, a new PK/PD tumor-in-host DEB-based model that includes the Simeoni TGI model [1], able to describe the drug action on the tumor mass, was developed. The model parameters provide a quantitative measure of these effects.

Methods: Pharmacological experiments using Harlan Sprague Dawley mice were performed in Nerviano Medical Sciences labs. In these experiments the tumor and mice net weights of control and treated animals were recorded at different doses and schedules. The PK profiles were derived from separated studies. Model parameters were evaluated by using the nonlinear weighted least squared algorithm as implemented in Matlab 2007b.

Results: The model has been tested in different experiments showing good capability in describing tumor growth as well as host body weight time-course in untreated and treated animals. Due to the model complexity, the physiological parameters of the tumor-free model have been estimated based on the growth data of typical HSD mice, subsequently the tumor-related and the drug-related parameters were estimated using the physiological values previously obtained in control animals.

Conclusions: The proposed model presents a new and complete approach for the simultaneous assessment of the anticancer drug efficacy and its impact on the clinical status of the animal represented by its body weight, providing in addition an evaluation of the direct effect of the drug on the net body weight. The possibility of predicting the behavior of the tumor and body weight within the same experiment under different conditions may provide a useful tool for identifying the most promising treatment schedules in terms of efficacy and toxicity balance. Moreover, even if the model has been tested and identified by using data of xenograft mice, its translational application turns out to be an interesting challenge in further investigations.

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Melanie Titze IV-29 A semi-mechanistic model to describe the bidirectional interaction between oncolytic reovirus and in vitro tumor growth of U87-glioblastoma cells

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Objectives: Oncolytic viruses (OV) like reovirus are replication-competent viruses, which are able to specifically infect and replicate in tumor cells and thus lead to rapid cancer cell death. Due to the dependency of viral replication on the number of susceptible tumor cells as well as the dependency of the tumor growth on viral destruction, the relationship between reovirus and glioblastoma cells reflects a highly complex interaction.
The objective of this analysis was to describe this bidirectional interaction between reovirus type 3 dearing and U87-glioblastoma cells. It was aimed to develop a semi-mechanistic mathematical model to describe the dynamics of *in vitro* tumor cell growth and reovirus replication and to depict the impact of reovirus treatment on tumor growth.

Methods: Relative tumor growth of human U87-glioblastoma cells was measured *in vitro* via cell viability using the MTT assay [1] for control (200 observations) and treatment group (150 observations) up to 144 hours after seeding. The effect of various reovirus doses (1 to 100 plaque forming units (PFUs)/cell) on tumor cells was investigated and viral titer were quantified up to 120 hours after infection (69 observations) via polymerase chain reaction (PCR) [2]. Model development was done sequentially by first investigating several models (e.g. Gompertz, exponential, logistic) to describe tumor growth. In the next step the model most accurately depicting tumor growth was linked to a viral dynamic model (VDM) adopted from literature [3]. Modeling was performed using non-linear mixed-effects modelling (FOCE-I method) in NONMEM V7.2.0 [4].

Results: Untreated U87-glioblastoma cell growth was best described by an exponential growth model. Viral dynamics were implemented in the VDM. In the VDM two different states of tumor cells were defined: uninfected tumor cells, which are growing exponentially and are infected by free virus particles and infected tumor cells, which are assumed to be no longer replication-competent and die at a first-order-rate constant and release new viruses with a first order rate constant. Goodness of fit plots and visual predictive checks showed an adequate performance of the model.

Conclusion: The developed VDM was capable of accurately describing the bidirectional interaction between tumor cell growth and reovirus dynamics. It can serve as a generic tool to systematically characterize and compare other OV and tumor cell lines.

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Swantje Völler IV-42 Age-Dependent Pharmacokinetics of Doxorubicin in Children with Cancer: Results of the EPOC-MS-001 Study

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Objectives: Although almost 60% of children diagnosed with cancer receive anthracyclines as part of their treatment, the knowledge on the pharmacokinetics (PK) of the drug in children is very limited. As doxorubicin was featured on the European Medicines Agency priority list for studies on off-patent paediatric medicinal products, a multicentre, multinational phase II PK study investigating a possible age-dependency in the clearance (CL) of doxorubicin in children with solid tumours and leukaemia was conducted. The data were analysed using a population PK model generated in NONMEM® 7.2.

Methods: Samples from 2 doxorubicin administrations in 101 patients treated according to the tumour-specific national or European therapeutic trial were collected with a particular focus on recruiting children less than 3 years. Data were analysed using NONMEM® 7.2, R, Xpose4 and a predefined stepwise strategy. A large number of covariates including patient characteristics, laboratory values (e.g. bilirubin, serum creatinine, alanine aminotransferase, serum albumin, haematocrit) and 17 single nucleotide polymorphisms were available in the study. Covariate modelling was performed using the stepwise covariate modelling strategy (SCM) integrated in PsN® with the linearization option. Using a linearized SCM was not possible for genetic polymorphisms as most were coded with three stages (wild type, heterozygous, homozygous). Therefore, each genetic polymorphism was tested separately for an effect on the CL of doxorubicin.

Results: A three compartment model was most suitable to characterise the PK of doxorubicin. All parameters of the population model were scaled to body surface area. The inclusion of age on the CL yielded a significant improvement of the model. No other patient-related covariate, including liver function, was found to influence the parameters of the model. Pharmacogenetic variants, including those in transporters and drug metabolizing enzymes, had no influence on pharmacokinetic parameters.
Using the mean estimated CL value for each individual, children less than 3 years had a lower CL (21.1 ± 5.8 l/h/m^2) than older children (26.6 ± 6.7 l/h/m^2) (p=0.0004), even after correcting for body size.

Conclusion: This study demonstrates an age-dependency in the clearance of doxorubicin in children. The results may be useful for refining dosage regimens in this patient group.

Wenyuan Xiong IV-49 PK/PD modeling of the c-Met inhibitor MSC2156119J to establish the recommended Phase II dose

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Objectives: To evaluate the dose/exposure/target inhibition/tumor growth relationship of MSC2156119J in order to determine the dose for the Phase II program. MSC2156119J is an orally administered, reversible, ATP-competitive, highly potent and selective c-Met receptor tyrosine kinase inhibitor.

Methods: Plasma PK and tumor c-Met inhibition data from Phase I solid tumor patients were analyzed by the population approach, using a prior structural model of target inhibition developed with data from KP4 xenografted mice. To help determine the recommended Phase II dose, human PK profiles and c-Met inhibition were simulated, aiming for a level of c-Met inhibition that achieves tumor regression in mice.

Results: In preclinical KP4 xenografted mice, c-Met inhibition in tumors (quantified as normalized phosphorylated c-Met expression [pMET]) was described by a turnover full inhibitory I_{max} model, and tumor growth inhibition was best described by the Simeoni model[1]. Simulations demonstrated that nearly complete pMET inhibition (≥95%) is required for tumor stasis or regression. In the first-in-human trial a 1-compartment linear model with first order absorption and a transit compartment best described the PK of MSC2156119J dosed from 30–700 mg. The turnover model developed from mice data was utilized to evaluate the level of c-Met inhibition in human tumors (1 pre-treatment and 1 on-treatment biopsy per patient). System turnover parameters (k_{in}, k_{out}) were set equal to the estimates in mice, while the potency parameter ($1/IC_{50}$) in humans was found to be 1.7 times higher than in mice. Assuming a 30% interindividual variability of IC_{50}, human simulations suggest that a 500-mg daily dose regimen could achieve continuous pMET inhibition of ≥95% in 90% of the population.

Conclusions: c-Met inhibition in human tumor lesions was described by a turnover model developed in KP4 xenografted mice, showing a 1.7-times higher potency in humans than in mice. With this translational modeling approach, a biologically active dose of 500 mg was proposed as the recommended Phase II dose for MSC2156119J.

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Huixin Yu IV-51 Integrated mechanism-based pharmacokinetic model for sunitinib and its active metabolite

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Objectives: Sunitinib is a multi-targeted tyrosine kinase inhibitor used in the treatment of several malignancies. The application of therapeutic drug monitoring (TDM) in clinical practice for sunitinib and its active metabolite SU12662 requires a pharmacokinetic (PK) model for adequate interpretation of data. However, published sunitinib models either neglected correlations between sunitinib and its metabolite [1] or were based on a very limited dataset [2]. Therefore, we developed a population PK model for both sunitinib and SU12662.

Methods: In this analysis, PK data of 70 patients were collected from three PK studies of sunitinib [3–5]. A mechanism-based PK model for sunitinib and SU12662 was developed incorporating pre-systemic metabolism using nonlinear mixed-effects modelling. According to the model, sunitinib is firstly absorbed by a first-order process to a hypothetical enzyme compartment, whereby sunitinib remains unchanged or is metabolised into SU12662. Subsequently, unchanged sunitinib and metabolite distribute to the central compartment. Sunitinib is further metabolised from the systemic circulation by the same enzyme. Allometric scaling based on body weight was applied for the estimation of clearance and volume of distribution. Graphical model assessment was performed by goodness-of fit plots and prediction-corrected visual predictive check (pcVPC).

Results: Both sunitinib as SU12662 PK were best described by one compartment models. Introduction of pre-systemic formation of SU12662 strongly improved the model (ΔOFV ~400). The clearances of parent and metabolite drugs were estimated at 35.3±1.59 $L \bullet h^{-1}$ and 17.3±0.98 $L \bullet h^{-1}$ for 70 kg individuals. Correlation efficient were estimated between inter-individual variability of both clearances, both volume of distributions, and between clearance and volume of distribution of SU12662 as 0.60, 0.38 and 0.30, respectively. The pcVPC indicated the developed model appropriately captured the PK and variability for both sunitinib and SU12662.

Conclusions: An adequate PK model for sunitinib and its active metabolite SU12662 has been developed and evaluated. Incorporation of pre-systemic metabolism strongly improved the model. Further studies in application of TDM service and PK-pharmacodynamic correlations can base on the developed PK model.

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Clare Gaynor I-12 Longitudinal Model-Based Meta Analysis of Sebum Excretion and Acne Severity

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Background and Objectives: While modelling individual-level data is preferred, often this is not an option when only summary-level data from literature sources are available. Model-Based Meta-Analysis (MBMA) [1,2,3] is an extension of the common practice of combining aggregate-level results from multiple clinical trials. Longitudinal statistical modelling can be used to incorporate covariates, enable the linking of short-term biomarker data with long-term clinical endpoints, integrate available internal and external data to characterise dose–response and time-course of drug effect.
Acne vulgaris affects an estimated 40-50 million people in the United States [4] and is the most commonly reported skin condition physicians encounter [5]. Biologically, acne is considered an inflammatory disease of the pilosebaceous unit with several distinguishing characteristics, including: excess sebum production; abnormal keratinocyte proliferation and desquamation leading to ductal obstruction; proliferation of *propionibacterium acnes*; and inflammation. A quantitative relationship between sebum excretion and acne lesions has been demonstrated in a previous landmark analysis [6]. The current work is being undertaken to establish the time course of sebum reduction and corresponding acne improvement across commonly prescribed systemic therapies.

Methods: A systematic survey of the literature was carried out. Studies involving topical or other non-systemic treatments (eg light therapies) were excluded. Non-linear mixed effects modelling (including testing Emax time-to-effect, placebo effect, influence of covariates and baseline status) was used to characterise the time courses of reduction in sebum excretion and acne improvement.

Results and Conclusion: The change in sebum excretion and acne improvement over time was adequately described. The MBMA allows the comparison of drug classes, allowing evaluation of the relative efficacy and onset of action and providing quantitative support for the efficient design of and interpretation of data from early signal of efficacy trials.

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Bojana Golubovic I-18 Population pharmacokinetics of sirolimus in adult kidney transplant patients

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Objectives: The aim of the study was to explore factors that significantly contribute to sirolimus (SRL) pharmacokinetic variability and develop population pharmacokinetic model using therapeutic drug monitoring (TDM) data.

Methods: TDM data of 25 adult kidney transplant patients were collected from patients' records. All measured concentrations were trough. Pharmacokinetic analysis was performed using NONMEM® software (version 7 level 2) and Perl speaks NONMEM (version 3.5.3). A one-compartment model with first-order absorption and elimination was used as a structural model. Volume of distribution and constant absorption were fixed to literature values.

Results: Estimated typical clearance (CL/F) value was 12.1 l/h. CL/F was significantly influenced by sirolimus dose and aspartate aminotransferase (AST) as liver function parameter. The relationship between CL/F and sirolimus was best described by the power model. According to developed population pharmacokinetic model, sirolimus CL/F was decreased, in average, for 35.3% in patients with AST greater than 37 IU/l. The stability of the model and predicted performance were confirmed by bootstrap method and numerical predictive check.

Conclusions: Dose and AST levels outside the upper reference range explained in part sirolimus interindividual variability. The results from the study allow individualization of SRL dosing in routine patient care, especially useful for patients with compromised liver function.

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Mario Gonzalez Sales I-21 Population pharmacokinetic analysis of tesamorelin in HIV-infected patients and healthy volunteers.

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Objectives: Tesamorelin is a synthetic analogue of growth hormone-releasing factor, which significantly decrease visceral adipose tissue and improve metabolic and patient-reported outcome parameters in HIV-infected patients with excess abdominal fat.[1] The aim of this study was to characterize the population pharmacokinetics of tesamorelin in HIV-infected patients and healthy subjects from data of two phase I clinical trials.

Methods: A total of 38 patients receiving subcutaneous tesamorelin doses of 1 or 2 mg administered daily during 14 consecutive days were included in the analysis. An open one compartment model with first and zero order absorption and first order elimination was developed to best describe the data using NONMEM VII. The effect of different covariates on tesamorelin pharmacokinetics was investigated. Model evaluation was performed using predictive checks and non-parametric bootstrap.

Results: Plasma clearance and its between subject variability (%) was estimated to be 1060 L/h (33.8). Volume of distribution was calculated to be 201 L (17.9). Age, body size measures and race were not related to tesamorelin pharmacokinetic parameters within the range of covariates studied. The fraction of tesamorelin absorbed by a first order process is 15.6% higher on day 14 compared to day 1. Predictive checks and non-parametric bootstrap demonstrated that the model is appropriate in describing the time course of tesamorelin plasma concentrations in both HIV-infected patients and healthy subjects.

Conclusions: An open one compartment model with first and zero order absorption processes and linear elimination is suitable to characterize the pharmacokinetics of tesamorelin. The fraction of tesamorelin absorbed by a first order process evolves with time. No clinically relevant covariates were identified as predictors of tesamorelin pharmacokinetics.

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Chihiro Hasegawa I-27 Modeling & simulation of ONO-5334, a cathepsin K inhibitor, to support dose selection in osteoporosis

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Objectives: ONO-5334, a selective inhibitor of cathepsin K, is a potential new treatment for osteoporosis. The pharmacokinetic (PK) and pharmacodynamic (PD) properties of ONO-5334 were assessed in order to support dose and formulation (immediate release tablet, sustained release tablet) selection for future trials.

Methods: The population PK-PD (exposure-response) modeling was performed using NONMEM based on plasma concentrations of ONO-5334 and PD markers. As PD markers, serum bone resorption markers and bone mineral density (BMD) responses were obtained in phase 1 and 2 trials, respectively, and used for modeling. With the use of the developed models, PD markers after administration of ONO-5334 SRT (sustained release tablet) as well as IRT (immediate release tablet) were simulated. BMD responses were simulated where only BMD response after administration of IRT had been studied to date, using PK model developed with SRT phase 1 data and exposure-response model developed with IRT phase 2 data.

Results: With the indirect response model ONO-5334 was assumed to inhibit the zero order production rate of serum bone resorption markers [1,2]. Relationships between ONO-5334 exposure and BMD responses were modeled using direct response models [3]. As an exposure metric, trough concentrations of ONO-5334 were selected which support the necessity of sustained plasma concentration over 24 hours. The simulation results showed that ONO-5334 SRT should provide comparable PD markers at a lower dose relative to IRT.

Conclusions: The modeling & simulation with PD markers led to the acquisition of useful information for selecting appropriate dose and formulation in the future trial.

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Niclas Jonsson I-42 A Population PK Analysis of Nebivolol and Valsartan in Combination Therapy

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Objectives: To characterize the population PK of nebivolol (*d*-nebivolol, *l*-nebivolol, nebivolol glucuronide) and valsartan as single drugs and as a fixed-dose combination (FDC), to characterize covariate relations and to generate predictions for PKPD modeling of sitting cuff-measured and 24-hour ambulatory blood pressure.

Methods: Population PK models were developed in NONMEM V7.2.0 [1] based on data from six Phase 1 studies and one Phase 3 study. A total of 893 individuals and 21066 observations were included in the analysis. The valsartan, *d*-nebivolol and *l*-nebivolol PK data were described by two-compartment models with first order absorption and lag-time. The nebivolol glucuronide model was driven by the observed total nebivolol and the predicted *d*-nebivolol and *l*-nebivolol concentrations, and was a two-compartment model with serial zero-first order absorption. The basic models were used as the basis for covariate model development. The impact of the statistically significant covariates on the area under the curve (AUC) and maximum concentration (C_{max}) were evaluated using univariate predictions. The ratios of AUC and C_{max} were computed for the 10^{th} and 90^{th} percentiles, or extreme categories for categorical covariates, of the observed covariate distribution.

Results: The final models provided adequate descriptions of the data as judged by graphical diagnostics and visual predictive checks. The covariates that were associated with the largest AUC and C_{max} ratios were study phase (1 versus 3) for valsartan and isoenzyme of CYP2D6 for *d*-nebivolol, *l*-nebivolol and nebivolol glucuronide. The CL/F for a typical extensive CYP2D6 metaboliser with mono-therapy were 14.2, L/h, 2098 L/h, 1179 L/h and 40.7 L/h for valsartan, d-nebivolol, l-nebivolol and nebivolol glucuronide, respectively. The corresponding values for poor metabolisers were 14.2 L/h, 97.7 L/h, 26.0 L/h and 3.8 L/h. There was no impact of co-administration on CL/F for d- and l-nebivolol while there was a ~20% increase for valsartan and nebivolol glucuronide.

Conclusion: The population PK of nebivolol and valsartan as single drugs or as FDC was successfully described by two-compartment models. A number of covariates were found statistically significant but only a subset had any substantial impact on AUC and $C_{max.}$ For d- and l-nebivolol the impact of co-administration was minimal and for valsartan and nebivolol glucuronide it was moderate.

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Takayuki Katsube I-48 Population PK/PD Modeling of Lusutrombopag, Thrombopoietin Receptor Agonist, in Healthy Volunteers for Exploring PK/PD Covariates

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Objectives: Lusutrombopag (also known as S-888711) is a small-molecule orally active thrombopoietin (TPO) receptor agonist. Lusutrombopag acts on human TPO receptors expressing in megakaryocytes and leads to thrombocytopoiesis. Lusutrombopag may have potency for the treatment of thrombocytopenia. Phase 1 studies in Japan and US were conducted in the development program. The aim of this study is to develop a population pharmacokinetic (PK)/pharmacodynamic (PD) model to describe plasma lusutrombopag concentrations and platelet counts following oral lusutrombopag doses and also to explore PK/PD covariates.

Methods: A 3-compartment model with first-order rate and lag time for absorption was used as a PK model. A PD model was developed based on semi-physiological model with production, maturation and elimination processes of blood platelet [1]. One platelet compartment with 3 transit compartments, a sigmoid E_{max} model and a feedback for production was used for describing platelet change with drug effect. A total of 2539 plasma concentration data and 1408 platelet count data in 78 healthy adult subjects following single or multiple (once daily for 14 days) doses of lusutrombopag were applied to the PK/PD model using non-linear mixed effects model approach by NONMEM [2]. PK and PD covariates were selected by screening using univariate regression to construct a full model, followed by backward deletion from the full model.

Results: The population PK/PD model well described time courses for plasma lusutrombopag concentrations and platelet counts. The model indicated good prediction and a lack of bias in goodness-of-fit plots and visual predictive check [3]. Body weight (WT) and ethnicity (Japanese or non-Japanese subjects) were significant as PK potential covariates. The empirical allometric relations for the effects of WT on clearance and volume of distribution were applied since the effect of ethnicity may be confounded with the effect of WT. WT was suggested to be the most influential PK covariate when assuming the allometric relations, while the ethnicity was not clinically significant. Any significant PD covariates were not found.

Conclusions: The difference of body weight between populations was suggested to result in differences in lusutrombopag PK profiles between the populations. The PD sensitivity for platelet response with the lusutrombopag effect was suggested to be similar between Japanese and non-Japanese subjects.

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Yo Han Kim I-53 Early characterization of ticagrelor using modeling and simulation analysis of the in vitro platelet aggregation test and human pharmacokinetic data

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Objectives: Ticagrelor is a reversible platelet P2Y12 receptor inhibitor which has been developed as a treatment of acute coronary syndrome. The objectives of these analysis were intended to provide a modeling and simulation methodology that could be used to characterize the pharmacokinetics(PK) and pharmacodynamics(PD) of ticagrelor.

Methods: Two studies were conducted: In vitro PD study, where we draw blood samples from 24 healthy male subjects and added ticagrelor and its active metabolite at various randomly selected concentration ranges. Then we measured platelet aggregation using an aggregometer. The in vitro pharmacodynamic data were analyzed using nonlinear mixed effects modeling (NONMEM) and response-surface pharmacodynamic model was built for ticagrelor.

In clinical PK-PD study, serial blood samples were collected from 12 healthy male subjects after single oral administration of ticagrelor 180 mg. Blood samples were processed for plasma concentrations and platelet aggregation test. Plasma concentrations of ticagrelor and its metabolite were measured by validated high performance liquid chromatography. Plasma concentration-time data were analyzed, using NONMEM to estimate population pharmacokinetic parameters and evaluate relationships between parameters.

Results: In the response surface model, the synergistic interaction was identified in the mixtures of ticagrelor and its active metabolite, AR-C124910XX. Although both ticagrelor and AR-C124910XX inhibited platelet aggregation, ticagrelor was more potent than AR-C124910XX with the IC50 of approximately 17% compared to AR-C124910XX in this study.

A three-compartment model with mixed zero order and first order absorption and lag time best described ticagrelor pharmacokinetics. Population estimates for absorption rate constant (k_a), central volume of distribution (V_2), systemic clearance (CL), peripheral volume of distribution (V_3), inter-compartmental clearance (Q), lag time ($ALAG_1$) and D_1 were 1.23 h^{-1}, 113 L, 29.7 L h^{-1}, 173 L, 18.8 L h^{-1}, 0.220 h and 0.476 h^{-1}, respectively.

Using the PD model from in vitro study and the PK model from clinical PK-PD study, the anti-platelet effect over time on ticagrelor was simulated and compared with real observed platelet aggregation data. This showed good agreement between prediction and observation, validating the PD model built from the in vitro study.

Conclusions: The current methodology could be applied to identifying optimal dosing regimens of anti-platelet therapy and could be useful for efficient novel drug development.

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Ryuji Kubota I-59 Population Pharmacokinetics of Ospemifene and Evaluation for Exposure Increase

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Objectives: To develop a population pharmacokinetic (PPK) model to assess influential factors on ospemifene pharmacokinetics; and to assess the potential risk of adverse event for the cases which may cause exposure increase.

Methods: A PPK model was constructed using pooled ospemifene concentrations. The followings were tested as covariates: age, race, body weight, BMI, albumin, ALT, bilirubin, and creatinine clearance. The expected changes in distributions of ospemifene exposures were assessed for the cases of administration to renal impairment subjects, administration to hepatic impairment subjects, co-administration with ketoconazole, or co-administration with fluconazole based on the Bayesian-estimated individual pharmacokinetic parameters. Safety information in a long-term safety trial was used to assess the potential changes in risks of adverse event regarding ospemifene exposure increase.

Results: A total of 7503 ospemifene serum concentrations from 1260 subjects were available for the PPK analysis. The PPK parameters estimates were 9.16 L/hr for CL/F, 34.3 L for V2/F, 16.4 L/hr for Q/F, 250 L for V3/F, and 0.522 hr^{-1} for ka based on the final model. The observed distribution in the long term safety study largely covered the expected distributions for administration to renal impairment subjects, administration to hepatic impairment subjects, and co-administration with ketoconazole, while insufficient exposure experience for co-administration with fluconazole. The incidence of adverse event was not associated with ospemifene exposure in the long-term safety study.

Conclusions: We have developed ospemifene PPK model. No relevant covariate was identified in the PPK analysis. The analyses support no dose adjustment for patients with renal impairment, patients with hepatic impairment or co-administration with CYP3A4 inhibitors, while caution should be executed for concomitant inhibition for CYP3A4 and CYP2C9.

Brigitte Lacroix II-01 Modeling the anti-drug antibody response in rheumatoid arthritis patients treated with certolizumab pegol

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Objectives: To characterize the rate and extent of the antibody response at the recommended dose schedules in rheumatoid arthritis subjects treated with certolizumab pegol (CZP), related to the drug exposure.

Methods: Subjects were flagged antibody-positive from the first incidence of anti-CZP antibody level >2.4 U/mL onwards. Antibody incidence was analyzed using a right-censored time-to-event model, based on data from 1752 subjects from phase II and phase III studies (population PK database [1-4]). Follow-up visits were included for subjects who did not enter the open-label follow-up studies. The analysis was performed in SAS using a parametric model with Weibull distribution. Potential covariate effects on the hazard rate were tested, including various CZP exposure measurements and concomitant use of methotrexate (MTX). Model selection was based on the Akaike information criterion and goodness of fit plots. Simulations to predict the rate and extent of antibody response at the recommended dose schedules were performed in TS2, based on the antibody model in addition to the population PK model and the dropout model [5] previously developed.

Results: Patients with lower trough concentrations were more likely to develop antibodies earlier. The analysis confirmed that the concomitant use of MTX (immunosuppressant) delayed the appearance of anti-CZP antibodies. The fraction of simulated antibody-positive patients obtained from the model was consistent with observed data, e.g. 10.7%(observed) vs 4 to 21% (simulated, weekly MTX dose from 5 to 20 mg) after 12 months of treatment every 2 weeks; 22.5% (observed) vs 25% (simulated) at 6 months for the worst case scenario, i.e. monotherapy and every 4 week dosing. The model over-predicted the rate of antibody formation when extrapolated beyond the observation period.

Conclusions: Higher trough concentration, which can be achieved with the use of higher doses and/or increased dosing frequency (e.g. loading doses) is a predictor of lower formation of antibody. The time to event model accurately predicted the incidence of anti-CZP response during the 6- to 12- month observation period of the studies from which it was derivated, however cannot be used to extrapolate the anti-CZP antibody response with long term treatment over 1 year.

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Kha Le II-07 Population PKPD Modeling of Geographic Atrophy Disease Progression, Target Mediated Disposition and Treatment Effect of Lampalizumab

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Objectives: To develop a population based model to understand geographic atrophy (GA) disease progression, PKPD relationship and the therapeutic effect of lampalizumab (anti-factor D) using data from the Phase Ib/II MAHALO study.

Methods: The PK, PD and efficacy data were obtained from a phase Ib/II, multicenter, randomized, single-masked, sham injection-controlled study of intravitreal administration of lampalizumab in patients with GA. The PKPD analysis used a nonlinear mixed effect modeling approach. The modeling was performed using a target mediated drug disposition (TMDD) model fitting serum and aqueous humor total lampalizumab and factor D (FD) data. The longitudinal natural GA disease progression and treatment effect of lampalizumab were modeled simultaneously using all patient data. Covariate analysis was performed to identify factors influencing the disease progression, and the drug dependent treatment effect. Simulations were performed to evaluate the predictive performance of the PKPD model.

Results: A combined ocular/serum TMDD model using quasi steady state approximation that takes into account fast turnover kinetics of FD in the eye, first-order drug clearance, complex internalization and transfer rate between ocular and serum tissues was shown to adequately describe the PKPD data. The natural GA disease progression measured by GA area as visualized by fundus auto-fluorescence imaging was well described by a linear growth model. The therapeutic effect of lampalizumab can be adequately described by a linear relationship between vitreous lampalizumab concentration and the slope of disease progression with time. A common variant previously associated with risk of age-related macular degeneration at the Complement factor I (CFI) locus was a significant covariate for both disease progression rate and lampalizumab treatment effect.

Conclusions: A population PKPD-efficacy model was developed to describe the longitudinal disease progression of GA, the disposition and treatment effect of lampalizumab. This model was used for evaluation of different dosing strategies.

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Yan Li II-12 PK/PD Modeling of Tumor Growth Inhibition in Xenograft Mice to Optimize Experimental Design and Improve Study Efficiency

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Objectives: In this study, the PK and PD data of a potent and selective mTOR kinase inhibitor were collected in xenografted tumor models in mice. A PK/PD model was developed to link drug exposures with inhibition of tumor growth to explore xenograft experiment designs and improve efficiency.

Material and Methods: PK data and tumor volume data collected from xenograft mice model under 7 different doses/regimens were used to develop PK/PD models. The indirect PD model was constructed to mimic physiologic processes of tumor growth and drug effect on the inhibition of tumor growth rate. In the PK portion of the model, there were a total of 5 fixed effect parameters and in the PD portion of the model, there were a total of 3 fixed effect parameters. Simulations were conducted to explore the minimal number of doses/regimen and optimal experiment designs to effectively capture drug effect.

Results: A 2-compartment PK model well-characterized the PK profiles of the mTOR inhibitor. The distribution of the mTOR kinase inhibitor is altered and distinct in xenograft mice as compared to healthy mice. In spite of this difference, PK from healthy mice adequately predict the tumor shrinkage in xenograft mice.

An indirect PK/PD model adequately captured the features of tumor growth and the anticancer effect of the mTOR kinase inhibitor, which provided reliable parameter estimates. Analyses shown that the net tumor growth rate defined as k_{growth}-k_{death} and drug effect of IC_{50} are the key drivers of the tumor shrinkage.

For the mTOR kinase inhibitor studied, multiple simulations and subsequent PK/PD analyses demonstrated that four treatment groups of QD doses plus a placebo treatment group could adequately characterize the tumor shrinkage and the resulted model could be used to predict alternative dose levels and dose regimens with good accuracy, additional doses/regimens provided redundant information.

conclusions: In our study with the mTOR kinase inhibitor, the PK exposure from the healthy mice was adequate to tumor shrinkage in xenograft mice. The indirect PK/PD link model well-captured the key drivers of the drug effect and adequately described the tumor shrinkage. The PK/PD modeling and simulation optimized the design and improved efficiency of the xenograft experiments.

Jos Lommerse II-15 PKPD model of erythropoietin and hemoglobin response in rats following administration of prolyl hydroxylase inhibitors

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Objectives: To develop a PKPD model describing the effect of small molecule prolyl hydroxylase (PHD) inhibitors on erythropoietin (EPO) and hemoglobin (Hb) response. To assess if a model based on short-term (1 day) preclinical studies is appropriate to predict long-term (4 weeks) treatment effects in order to accelerate candidate compound selection.

Methods: Small molecule PHD inhibitors mimic hypoxia mediated Hypoxia-Inducible Factor (HIF) stabilization and thereby activate EPO transcription and translation, leading to reticulocyte proliferation and, as a consequence, increasing hemoglobin levels. PHD inhibitors have the potential as a therapy for chronic anemia [1]. An indirect-response model was used to describe the increase in EPO following one or two doses of two small molecule PHD inhibitors to rats. The delay of the EPO response is captured by a series of transit compartments and an initial lag time after the very first dose. NONMEM v7.1 with FOCE INTER was applied for the estimation of model parameters. The PK-EPO model has been combined with a previously published model relating EPO concentrations to Hb change in rats [2]. The reported parameters of this EPO-Hb model were maintained and the Hb response after 4 weeks of treatment were simulated and compared to actually observed data from a different experiment.

Results: The rat PK-EPO model allowed for the simultaneous estimation of compound-independent (i.e. system-specific) parameters, such as the EPO elimination rate (KOUT) or the maximum stimulatory effect (SMAX). For both PHD inhibitors the initial delay of the EPO response was very similar (

Conclusions: PK and EPO data obtained from short-term experiments provide sufficient information to predict effects of small molecule PDH inhibitors on Hb levels after 4 weeks of treatment. This provides an excellent basis for rapid in vivo compound evaluation to screen clinical candidate compounds.

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Mats Magnusson II-18 A Population PK/PD Analysis of Nebivolol and Valsartan Combination Therapy

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Objectives: To develop population PK/PD models that describe the effects of placebo, nebivolol and valsartan as single drugs and as a fixed-dose combination (FDC) on both sitting cuff-measured blood pressure (BP) and 24-hour ambulatory measured BP (diastolic and systolic BP), and to use the model to further simulate possible combinations of dosages.

Methods: Population PK/PD models were developed in NONMEM V7.2.0 [1] based on data from the Phase 3 study (NAC- MD-01), utilizing estimates of exposure for each individual derived from a population PK model. The exposure-response population included 761 patients for the sitting cuff-measured BP and 746 patients for ambulatory measured BP. The BP lowering drug effects of nebivolol and valsartan were described by inhibitory Emax models with a parameter (alpha) to account for the interaction between the compounds. The diurnal rhythm in the ambulatory BP data was described by the sum of cosine functions [2].

Results: For the sitting cuff-measured BP model, total effect was comprised of the drug effect and placebo effect. There was no detectable placebo response in the ambulatory BP data. The maximum drug effects were 13 mmHg for sitting cuff-measured BP, and 14 and 19 mmHg for diastolic and systolic ambulatory measured BP, respectively. The exposure-response relationships were statistically significant in the valsartan and nebivolol monotherapy arms as well as in all FDC arms, suggesting increasing efficacy with increasing PK exposures. The alpha parameter was estimated to be positive in all sitting cuff-measured and ambulatory measured BP models, and this effect was further characterized as partially additive.

The PK/PD model was used to simulate possible dosages in mono-, and combination therapy, including that of dosing strengths that were not studied in the NAC-MD-01 study. The model-predicted change from baseline in diastolic and systolic BPs demonstrated that all studied FDC doses (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg, and 40/320 mg) had greater BP reductions compared to their monotherapy components in a partially additive manner. An exposure response relationship was also evident between the FDC dose groups.

Conclusions: Modeling and simulation of nebivolol and valsartan combination therapy demonstrate a partially additive effect on diastolic and systolic sitting cuff-measured BP as well as on diastolic and systolic 24-hour ambulatory measured BP among all FDC doses studied.

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Matilde Merino-Sanjuán II-23 Simulation of Plasmatic Taurine Levels In Well And Undernourished Rats After Enteral Diet Administration.

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Objectives: It has been established that 5-15% of the general population, 40% of patients admitted to hospital and 60% of nursing home residents in the European Community are malnourished or at risk of malnutrition[1, 2]. Taurine, a conditionally essential aminoacid involved in numerous biological processes, is a regular component of commercial enteral diets provided to caquectic patients, although little is known about its pharmacokinetic (PK) from these formulations[3]. The aim of this study was to describe the behavior of taurine administered in two enteral commercial diets in well and undernourished rats and analyze the predictive capacity of a PK model developed in a previous study simulating WN and UN groups.

Methods: Wistar rats were randomly distributed in two groups - WN (well-nourished) and UN (undernourished) - and were fed with different pellet diets for 23-26 days[4]. During this time, weight was recorded daily and serum albumin was registered weekly. After this time, Isosource –ST™ and T-Diet Plus™ diets were orally (PO) administered to WN and UN rats (N=76). Plasma samples were collected for taurine and were analyzed by HPLC. The simulated concentrations were obtained by 100 simulations of WN and UN animals based on a previous developed two compartmental model using nonlinear mixed effects software (NONMEM 7.0)[4]. A visual predictive analysis was developed to determine if the PK model used reproduced the aminoacid plasma concentration in WN and UN groups.

Results: A two-compartment population PK model with zero order endogenous formation (Velo), passive absorption (ka), first order kinetics distribution (K_{12}, K_{21}) and nonlinear elimination with parallel Michaelis-Menten excretion and reabsorption processes best described taurine pharmacokinetics administrated as a solution. The main PK parameters are shown: ka=1.19 h^{-1}, Velo=13.70 mg/h, Vc=0.042 l, K_{12}=2.61 h^{-1}, K_{21}=0.73 h^{-1}, Vm_{sec}=192.0 mg/l·h^{-1} Km_{sec}=399.0 mg/l, Vm_{reabs}=16.9 mg/l·h^{-1}, Km_{reabs}=96.1 mg/l, FDNVms=0.91. Visual predictive check plots (VPC) after the administration of the doses of taurine contained in the enteral diets assayed showed reasonable good results.

Conclusions: Simulation of taurine plasma concentration provides a useful tool to describe the levels of taurine in well and under-nourished animals. This pre-clinical PK model also provides evidences to assess if the supplementation of taurine in enteral diets triggers an increment of taurine plasmatic concentrations.

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Enrica Mezzalana II-25 A Target-Mediated Drug Disposition model to quantify the relationship between Otelixizumab in vitro concentration and TCR/CD3 engagement

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Objectives: Otelixizumab is a monoclonal antibody (mAb) directed against CD3ε, a protein forming part of the CD3/T-cell receptor (TCR) complex on T lymphocytes [1]. An *in vitro* culture system was proposed to investigate Otelixizumab binding characteristics in a static situation. Specifically, the objective of this work was to quantify the relationship between Otelixizumab *in vitro* concentration and TCR/CD3 engagement. Within this framework, the Target Mediated Drug Disposition (TMDD) hypothesis [2] was investigated for Otelixizumab disposition.

Methods: A wide range of doses was proposed in order to detect and properly quantify nonlinearities in Otelixizumab PK. For this purpose, peripheral blood mononuclear cells (PBMCs) from two donors were incubated with titrated Otelixizumab initial concentrations in the range 0.001-10 µg/ml. To investigate the kinetics of CD3/TCR re-expression, cells were washed on day 2 to remove exogenous Otelixizumab and thereby allow CD3/TCR complex re-expression to be monitored. At each time point free, bound and total TCR/CD3 expression on both CD4+ and CD8+ T cells and the amount of free antibody in the supernatant were measured. A TMDD model [3] accounting for Otelixizumab binding on both CD4+ and CD8+ lymphocytes was proposed with the intent to describe in vitro experimental data. Analyses were conducted using NONMEM version 7.2. Final models were selected based upon change in OFV, precision of estimates and diagnostic goodness-of-fit plots.

Results: All parameters were estimated with reasonable precision (<40%). The proposed Target Mediated Drug Disposition model well captured the PK and PD profiles of Otelixizumab. No significant difference was found in the binding constants for binding on CD4+ or CD8+ lymphocytes (Kon=51.5/nM/day and Koff=4.64/day). The estimated values for binding parameters suggested high Otelixizumab affinity to TCR/CD3 receptor (KD = Koff/Kon = 90 pM). Estimated internalization rates (Kint4=1.26/day and Kint8=1.29/day) were 5 times higher than degradation rates (Kdeg4=0.273/day and Kdeg8=0.275/day).

Conclusions: The TCR/CD3 receptor has been shown to have a major role in determining the non-linear PK of Otelixizumab. A TMDD model accounting for Otelixizumab binding to TCR/CD3 on both CD4+ and CD8+ lymphocytes successfully captured the PK and PD *in vitro* data, confirming that the assumptions of this model are reasonable for Otelixizumab.

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Raymond Miller II-26 Modelling and simulation of the activity of intrinsic Factor Xa following edoxaban treatment

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Objectives: To describe the relationship between the exposure of Edoxaban (a direct Factor Xa inhibitor) and the activity of intrinsic Factor Xa (iFXa) and bleeding events.

Methods: A population PK model of edoxaban was built using 13 Phase I and 5 Phase II studies including 11,444 PK samples from 1,624 subjects. Individual post hoc concentration values were used to model the iFXa data from a 3-month Phase II study[1] evaluating the safety of the four doses of edoxaban (30mg QD, 60mg QD, 30mg BID, and 60mg BID) in patients with NVAF compared to warfarin. The iFXa was determined with a two-stage chromogenic method (Biogenic, Tokyo, Japan). A dynamic binding model was fit to the iFXa data from 585 patients who received edoxaban. For both the PK and PD models of edoxaban, the first order conditional estimation with interaction (FOCEI) estimation as implemented in NONMEM V.7.2 was used to obtain estimates of the model parameters and the variance-covariance matrix. Logistic regression analysis was then employed to find the best predictor for the bleeding event.

Results: A two-compartment PK model adequately described the plasma edoxaban concentration data from the 18 studies. The dynamic binding model fit the iFXa data better than other PD models (eg, equilibrium model) due to the mechanism of edoxaban binding to the intrinsic FXa. Logistic regression analysis showed that the time duration of iFXa suppressed at a certain threshold value or lower best correlated with the bleeding events observed from the Phase II study, and that the observed bleeding order matched the order of the time duration for the threshold of 15% activity: 30 mg QD (5.5 % / 9.2 hr), 60 mg QD (7.3 % / 13.7 hr), 30 mg BID (12.7 % / 18.8 hr), 60 mg BID (18.3 % / 21.6 hr). Therefore, 60 mg QD could be administered with less risk of bleeding than 30 mg BID at the same daily dose of 60 mg.

Conclusions: The established PK and PD models of edoxaban have good predictability with respect to the observed data. The prolonged period of iFXa suppression, despite the same total daily dose, may provide a biological explanation to the greater bleeding risk observed from 30mg BID compared to 60mg QD. The 60mg QD and 30mg QD regimens showed similar and less bleeding risk to the warfarin control treatment (8.0%), respectively, and were chosen for the phase 3 trials [2,3].

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Dirk Jan Moes II-28 Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in liver transplant patients

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Objectives: The once daily formulation of tacrolimus is an important immunosuppressive drug metabolized by CYP3A enzymes. Inter-patient variability in tacrolimus metabolism has been related to both the *CYP3A4* and *CYP3A5* genotype. However, in liver transplants, both donor and recipient genotypes may affect pharmacokinetics. The aim of this study was to investigate the effect of *CYP3A4*22* and *CYP3A5*3* of both donor and recipient on once daily tacrolimus pharmacokinetics in liver transplant recipients.

Methods: Stable liver transplant patients receiving once daily tacrolimus (N=49) were included. Blood concentrations were determined with LC-MS/MS. Population pharmacokinetic analysis was performed and demographic factors, *CYP3A4*22* and *CYP3A5*3* were tested as covariates. Moreover a limited sampling model was developed.

Results: Tacrolimus once daily formulation pharmacokinetics was best described by a two compartment disposition model with delayed absorption. *CYP3A5*1* carrying recipients engrafted with a *CYP3A5*1* carrying liver had a 1.65 fold higher clearance compared to non-carriers. *CYP3A5*1* carrying recipients engrafted with a *CYP3A5*1* non-carrying liver or vice versa showed a 1.13 fold higher clearance compared to non-carriers. *CYP3A4*22* was not associated with once daily tacrolimus pharmacokinetics. A limited sampling model using 0, 1 and 3 hours postdose resulted in a significantly improved prediction of tacrolimus exposure.

Conclusions: Dose adjustments based on *CYP3A5* genotype of both donor and recipient are indicated. In contrast *CYP3A4*22* appears not suitable as biomarker for tacrolimus pharmacokinetics. 0, 1 and 3 hours postdose as limited sampling model can be used to accurately estimate tacrolimus once daily formulation exposure in liver transplantation.

Sung Min Park II-44 Population pharmacokinetics and CYP3A5 genotype effect of S-amlodipine in healthy Korean male subjects

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Objectives: Amlodipine as a calcium channel blocker that is prescribed for the management of hypertension and angina pectoris and is known to have large inter-individual pharmacokinetic (PK) variability. The aims of this study were to develop a population PK model of S-amlodipine in healthy Korean subjects and identify whether *CYP3A5*3* plays a significant role in the disposition of S-amlodipine, compared with *CYP3A5*1*.

Methods: The PK model was built using data from a randomized, open-label, crossover study having two-period and two-treatment in 30 healthy male adults. All subjects were received either the test or reference formulation as a single 2.5-mg oral dose of S-amlodipine, followed by a 3-week washout period and administration of the alternate formulation. Blood samples were drawn at 0 (pre-dose), 1, 2, 4, 5, 6, 8, 12, 16, 24, 48, 96, 144, and 216 hours. S-amlodipine plasma concentrations were analyzed by LC/MS/MS. SNP genotyping was performed by an ABI 7900-HT. A population PK analysis was implemented in NONMEM (Ver. 6.2).

Results: The population PK model was best fitted by 2-compartment model with zero-order absorption and first-order elimination. Parameter estimates were as follows; k_e, 0.018 h^{-1}; V_c/F, 1890 L; V_p/F, 414 L; Q/F, 58.7 L/h; $D1$, 4.95 h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model. There were no significant covariates affecting PK parameters. Disposition of S-amlodipine was not affected by *CYP3A5* genotype.

Conclusions: A population PK model was successfully developed and reasonable parameters were obtained. The reason why the CYP3A5 genotype showed no statistically significant effect on the disposition of S-amlodipine might be from the small sample size. The estimated parameters may be applied to determine the optimal dosage regimens of S-amlodipine.

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Nathalie Perdaems II-47 Translational PKPD modeling of a cardiovascular drug and the interrelationship between blood pressure and heart rate in animals and human

Nathalie Perdaems
Technologie Servier

Objectives: To apply a translational modeling approach to help the first in man.

A reflex tachycardia was observed in rats due to the decrease of the blood pressure, so the administration of a modified release formulation in human is discussed in order to limit this increase of heart rate.

Methods: Interrelationship between blood pressure, cardiac output and total peripheral resistance have already been described in the literature using mechanism-based models [1, 2, 3].

A simple mechanism-based model is under development in rats to describe the relationship between the blood pressure and the heart rate in order to describe the reflex tachycardia due to the decrease of the blood pressure. The mechanism-based model approach will be then applied to other species (at least human).

When the interrelationship between blood pressure and heart rate will be established, the effect of the S compound will be added using a PKPD model. The PKPD model will be first developped in rats and then transposed into human .

So, the effect of the absorption rate of the drug will be tested in order to limit the reflex tachycardia in human.

Results: This modeling exercise is still in development.

Conclusions: This modeling exercise is still in development.

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Philippe Pierrillas II-49 Preclinical evaluation of the dose-concentration-marker-tumor growth relationship of a new pro-apoptotic compound using population PK-PD modeling

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Objectives: A new compound (*S*), in non-clinical settings, has been designed as a pharmacological tool to restore apoptosis functions. Preliminary analyses revealed nonlinearity in the relationship between dose, exposure, biomarker and tumor size. Based on data issued from *in vitro* experiments and *in vivo* studies in mice, the aim of this work was to build a semi-mechanistic PK-PD model to characterize the relationships between dose, plasma concentration, caspase activity and tumor size.

Methods: Data from preclinical studies evaluating *S*, administered either intravenously or *per os*, in xenograft mice were considered: 218 measures of concentrations (after single and repeated administrations), 54 of caspase activity and 64 measures of tumor size were modeled simultaneously. The pro-apoptotic effect was defined as an enhanced activation of caspase. The effective concentration was linked to plasma concentration, considering the unbound fraction and target affinity, derived from *in vitro* experiments. Tumor growth inhibition was then linked to caspase activity. Parameters were estimated using NONMEM 7.3 and model development was guided by residual- and simulation-based diagnostics.

Results: PK, caspase kinetics and tumor dynamics were successfully characterized by the proposed PK-PD model: the non-linear plasma pharmacokinetics was best described by a two-compartment disposition model with both saturable absorption and elimination. Auto-induction of elimination was characterized by stimulation of metabolism of *S* [1]; effective concentrations were expressed from the unbound plasma concentrations, through an interface model, defining a threshold level [2]; inhibition of the pharmacological target was resulting from a receptor occupancy model triggered by the effective concentration; caspase activity was modeled as an indirect effect model, whose production is inhibited by the target; tumor growth dynamics was modeled by a bi-phasic model [3],inhibited by an all-or-nothing effect of caspase. Model evaluation by goodness-of-fit and Visual Predictive Check, were satisfactory.

Conclusions: A semi-mechanistic approach, based on experimental mice data and *in vitro* parameters provides an interesting tool to quantify the expected antitumor effects and to propose an optimal dosing regimen in mice. In further steps, the pharmacodynamic model will be linked to a physiologically based pharmacokinetic model, to provide an extrapolable model for *S* to other species.

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Hyerang Roh II-58 Characterization of Nocturia Patient's Urination Pattern and Assessment of Drug Treatment Using Joint Ordered Categorical Model

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Objectives: Nocturia occurs in about 70% of the elderly, lowering the quality of life seriously. However, due to the lack of understanding of the disease and objective tool, drug effects have been evaluated based on empirical bases. [1-4] This study aimed to quantitatively characterize the diurnal pattern of nocturia's main symptoms and to develop a model for quantitative assessments of drug effects given routine clinical data.

Methods: Data were collected from Frequency Volume Chart of 20 male outpatients with severe nocturia (≥ 3 urinations/night) evaluated over 3 periods, before treatment (Period 1), after 1 month of mono-therapy of tamsulosin (Period 2), and after 3 months of combination therapy of tamsulosin and solifenacin (Period 3). The urination frequency (FREQ) and the average urine volume per void (FBC, functional bladder capacity) for every 2 hour interval within the 24 hour period were analyzed as ordered categorical variables with differential odds models after being categorized. The model was chosen by maximizing the joint likelihood of the two categorical variables using NONMEM 7.2. The joint ordered categorical model thus built was used to describe the data, where no-urination category was analyzed in the frequency model only, as it was redundant in the volume model [5, 6].

Results: Each variable was divided into 3 categories, 0, 1, 2 urinations for FREQ, and <100, 100-200, ≥200 mL for FBC. For period 1, the baseline logit was best described by a constant (category ≥ 1) decreased by a circadian function with 24-hr period (category ≥ 2) for FREQ, and a circadian one with 12-hr period decreased by a constant for FBC. Drug effects for FREQ were best described by an exponential decay (period 2) plus an additional constant (period 3) added to the baseline logit, allowing for a change in the baseline mesor for period 3 for FBC, yielding 0.17/hr and -0.34 for exponential decay rate and additional constant decrease for FREQ and 40% increase in the mesor for FBC. When drug effects were assessed by symptom improvements in nocturia, the probability of no-urination category at nighttime increased from 16% up to 44% and 52% in period 2 and 3, respectively, while that of large FBC category increased from 26% up to 41% in period 3.

Conclusions: These results demonstrate the feasibility of applying the proposed method to quantitative understanding of nocturia characteristics and objective assessment of drug effects with less cost and greater accessibility.

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[6] Pharmacometrics(2007), Ene I. Ette, 24. Pharmacometrics PK/PD Analysis of Binary (Logistic) Outcome Data & 25. Population Pharmacokinetic/ Pharmacodynamic Modeling of Ordered Categorical Longitudinal Data

Franc Andreu Solduga III-06 Pharmacokinetic modeling of enterohepatic circulation of mycophenolic acid in renal transplant patients.

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Objectives: (i) To establish an integrated population pharmacokinetic (PPK) model for MPA, MPAG and AcMPAG in renal transplant recipients on an immunosuppressive regimen with MMF and cyclosporine (CsA) or macrolides (tacrolimus or sirolimus); (ii) to quantify the effect of MRP2 polymorphism and CsA treatment on MPA and its metabolites disposition.

Methods: 56 patients received MMF 1g twice daily in combination with CsA or macrolides. 2038 (MPA), 2054 (MPAG) and 1043 (AcMPAG) concentration-time values were simultaneously analyzed with NONMEM 7.2[1] using PsN v3.5.3 and R code v3.0.1. The FOCE-I method was used for estimation and internal validation was performed with VPC[2], PPC[3] and NPDE[4].

Results: Two two-compartment models for MPA and MPAG and a one-compartment model for AcMPAG, with time-lagged first-order transformation/absorption process, provided the best fit of the data. MPA was converted to MPAG and AcMPAG according to two parallel first-order elimination processes. The metabolic clearance of MPA was estimated by CL_{MPA}·fm + CL_{MPA}·(1-fm), where fm was the ratio of the fraction of MPA metabolized to MPAG. Enterohepatic circulation (EHC) was modeled with a first-order transfer rate constant (K_T) from the MPAG central compartment to the absorption site. Both metabolites showed a linear elimination. Between-patient variability was associated with CL_{MPA}, CL_{MPAG}, CL_{AcMPA}, Vc_{MPA}, and K_T. Between-occasion variability could not be included in the model due to high computational intensity. Residual error of the three compounds was adequately described by an additive model for logtransformed data.

MPAG and AcMPAG plasma clearances significantly decreased with renal function. No significant influence of multidrug-resistant-associated protein-2 C24T single-nucleotide polymorphism was found. The model adequately predicted the increase in MPAG/AcMPAG exposures in CsA and macrolide patients with decreased renal function. As a consequence, higher MPA exposures in macrolide patients were observed compared to CsA patients. Increased MPA exposures with renal function changes from 25 to 10ml/min in macrolide patients was found by the enhanced MPAG enterohepatic circulation. The lowest-percentage of EHC occurred with the highest $C_{troughCsA}$ and renal function values.

Conclusions: A PPK model has been developed to describe MPA and its major metabolites disposition, supporting CL_{CR} and co-medication-tiered dosing regimen for MMF to standardize exposure during the post-transplant treatment.

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Ioanna Athanasiadou III-10 Hyperhydration may alter urine pharmacokinetic profile of drugs: A simulation study using budesonide as model drug

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Objectives: To study the effect of hyperhydration on the urine pharmacokinetic profile of the model drug budesonide (BDS) and its possible implication as a doping masking procedure used by athletes.

Methods: A one-compartment PopPK model was constructed from non-compartmental PK values taken from literature [1], using the methodology described in [2]. This model was implemented in MatLab SimBiology toolbox, and 1000 subjects administered a single per os dose of 9 mg BDS, were simulated. The renal regulation of urine volume [3] and the conditions of water retention [4] were taken into account for urine production modelling. The normal BDS PK urine profiles and additional PK profiles after 10, 20 and 30 ml of water consumption/kg of body weight, were generated, in order to simulate the effect of hyperhydration on urine PK profile of BDS for 3 hydration levels. Simulation of urine sampling collection schedule was also performed and used to evaluate the effect of hyperhydration on measured BDS and its primary metabolites (i.e. 16α-hydroxyprednisolone and 6β-hydroxybudesonide) urine concentration levels during doping control analysis.

Results: Simulation analysis revealed that BDS/metabolites urine concentration at the time points of hyperhydration was significantly decreased compared to the normal profile; the difference was more pronounced as the hydration level increased. In addition a 3.5-8.0% of the predicted urine BDS/metabolites concentrations were found below the minimum required performance level (30 ng/mL) according to WADA guidelines. This percentage is approximately 3.0% even for normal PK profile and is probably the result of the circadian rhythm of urine production. The effect of BDS dose and different hyperhydration intake scenarios on BDS PK urine profile is also studied.

Conclusions: Clear effect of hyperhydration on BDS/metabolites urine profile was shown, supporting the hypothesis of its possible application as a doping masking procedure by athletes. These findings may lead to optimal design of the time schedule of urine sampling during anti-doping control allowing the detection of doping agents if hyperhydration could be used by athletes as a masking procedure. To verify this hypothesis, a single dose BDS PK study in healthy male athletes with or without hyperhydration is designed, based on the present simulation analysis.

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Jan Berkhout III-14 Mechanism-based approaches to the analysis of comparative effectiveness in osteoporosis

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Objectives: Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the US alone, approximately 44 million people are affected by osteoporosis and low bone mass. Several pharmacological treatments exist for the prevention of osteoporosis such as hormone replacement therapy and bisphosphonates. However, limited data exist on the comparative effectiveness (e.g. providing evidence on the effectiveness, benefits, and harms of different treatment options) of these treatments between populations within clinical trials and under the real life circumstance. Recently, a mechanistic osteoporosis framework was developed to describe disease progression together with treatment effects. This model was applied to clinical data from post-menopausal women receiving various doses of tibolone or calcium [1]. This research project will use the mechanistic model to address the following research questions:

1. Can the existing disease system model for osteoporosis be extended to treatment with the bisphosphonate drug alendronate?
2. Use the mechanism-based model in combination with data from a cohort study in the elderly population (The Rotterdam Study, RS) to explore what part of the observed variation in bone mineral density (BMD) in the real-life population is due to treatment effect and what part by other covariates.
3. Fracture data available from the RS will be used to extend the model to predict clinical outcome.

Methods: To address the first research question the previously developed model will be applied to clinical trial data from post-menopausal women receiving the bisphosphonate alendronate and/or conjugated estrogen [2]. The disease model will be used to obtain a further mechanism-based description of the disease processes following alendronate treatment. The RS is a unique population based cohort of elderly subjects with extensive long term follow-up data that will be used to address the second and third research questions. Both questions will contribute to a more complete and mechanism-based description of the whole trajectory of the disease and the corresponding fracture incidence.

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Karl Brendel III-23 Population Pharmacokinetic modelling for a molecule S and its glucuronide metabolite including enterohepatic recycling

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Introduction: Enterohepatic recycling (EHC) occurs when there is biliary excretion followed by intestinal reapsorption of a compound, sometimes with hepatic conjugation. Multiple peaks in a plasma concentration profile may be a consequence of this recycling. A change-point model, which is a model in which a parameter's value discontinuously changes at a given time is often used to mimic EHC (1).

Objectives: To develop a population PK model for both the parent and its main active metabolite including a EHC for the metabolite.

Methods: Data after single administration, coming from 3 Phase I study, including a total of 61 healthy volunteers, were used to build a population PK model for both the parent (S1) and its main active glucuronide metabolite (S2).

The high molecular weight of both compounds, the glucuronidation of the metabolite and the time of second peak around meal-time, suggest the hypothesis of EHC to describe the second peak in the plasma concentration-time profile. EHC was implemented with a change-point model using model event time parameter (MTIME) directly implemented in NONMEM. Several model structures and assumptions (e.g. first pass effect) were tested during model building. The adequacy of the model to describe the data was assessed based on asessement of uncertainty on parameter estimates (RSE), and on advanced evaluation methods such as VPC and NPDE. Estimation of the population parameters was performed using NONMEM 7.2.

Results:S1 concentration-time data were described by a 2-compartment model with first-order absorption with no renal elimination. S2 data were also described by a 2-compartment model linked to the central compartment of S1. EHC was modelled with a semi-mechanistic model where a fraction of S2 from the central compartment was excreted into a gall bladder compartment with a first-order rate constant and a periodic drug release from the gall bladder using MTIME. Some parameters like the fraction going to gall bladder were fixed due to the lack of information and therefore model identifiability. Expected first-pass effect was not identified. The RSE, VPC and NPDE were satisfactory for both S1 and S2.

Conclusions: In order to implement a EHC, a change-point model was used to describe the concentration-time data of a parent and its glucuronide metabolite. Further studies (e.g. IV microdose study) will be performed to better characterize PK parameters (e.g. first pass effect, intrinsic clearance of S2).

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Ana Catalan-Latorre III-30 A Mechanistic Population Pharmacokinetic Model For Taurine In Well And Undernourished Rats

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Objectives: Protein-energy undernutrition (PEU) can seriously compromise the outcomes of other pathologies since pathophysiological derangements in patients with PEU have a profound impact on absorption, protein binding, metabolism and elimination of drugs[1-3]. Taurine is a conditionally essential aminoacid involved in numerous biological processes and its needs increase in response to pathological conditions[4]. The aim of this study was to perform a PK modelling to describe the behavior of taurine in well-nourished rats and analyze the influence of PEU on the PK parameters of taurine in undernourished rats.

Methods: Wistar rats were randomly distributed in two groups -WN (well-nourished) and UN (undernourished) - and were fed with different diets for 23-26 days[5]. During this time, weight was recorded daily and serum albumin was registered weekly. After this time taurine was administered intravenously (IV) or orally (PO) to WN and UN rats at different doses: 1, 10, and 100 mg (N=68). Plasma samples were collected for taurine and were analyzed by HPLC. Population pharmacokinetic modelling was performed using nonlinear mixed effects software (NONMEM 7.0). Several distribution and absorption models were explored in combination with dose and/or time covariate effects. Covariates such as nutritional status, serum albumin, body weight and score of undernutrition were used.

Results: A two-compartment population pharmacokinetic model with zero order endogenous formation, passive absorption, first order kinetics distribution and nonlinear elimination with parallel Michaelis-Menten excretion and reabsorption processes best described taurine pharmacokinetics. When models were scaled for malnutrition, undernutrition acted as covariate reducing the Vmax of the active elimination process. Goodness of fit plots (GOFP) showed reasonable good results. The main PK parameters are shown: ka=1.19 h^{-1}, Velo=13,70 mg/h, Vc=0.042 l/h, K_{12}=2.61 h^{-1}, K_{21}=0.73 h^{-1}, Vm_{sec}=192.0 mg/l·h^{-1} Km_{sec}=399.0 mg/l, Vm_{reabs}=16.9 mg/l·h^{-1}, Km_{reabs}=96.1 mg/l, FDNVms=0.91.

Conclusions: Data analysis showed linear absorption and distribution, and non-linear elimination processes for taurine. Elimination of taurine was reduced in undernourished animals, suggesting that the reabsorption process via the secretion transporter was modified in this group. Modelling provides a useful tool to describe the levels of taurine and offers a robust method to understand the changes in PK ocurred in undernorishment.

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Emmanuelle Comets III-45 Population pharmacokinetics of mycophenolate acid and its metabolite in liver transplant patients

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Objectives: The objective of this work was to develop a pharmacokinetic (PK) model for mycophenolate acid (MPA) and its main active metabolite, phenolic glucuronide metabolite (MPAG), in patients given mycophenolate mofetil (MMF) in association with low doses of tacrolimus and steroids, to prevent graft rejection after hepatic transplantation.

Methods: The MMF-FK clinical trial was designed to investigate the benefits of co-administering MMF to reduce daily doses of tacrolimus in liver transplant recipients[1]. Patients were randomised to receive either tacrolimus therapy in conventional doses, or half doses of tacrolimus in combination with oral MMF, given as 1.5g twice daily for 6 weeks, then 1g twice daily. PK samples were collected 3 weeks (PK1) and 3 months (PK2) after transplantation. The Kehr drain implanted in the bile duct after transplantation was declamped at PK1 and clamped at PK2. The data were analysed through nonlinear mixed effect models, using Monolix 4.2.2[2].

Results: PK was collected in 27 patients, 20 of which had measurements on both occasions. The PK was well described by a 2 compartment model for MPA and a one-compartment model for MPAG, with enterohepatic recycling. The parameters defining MPAG recycling were estimated by a grid approach. MPA was mainly eliminated after metabolism to MPAG. At PK2 the amount of MPAG recycled was 10%, and decreased by about 50% at PK1 when the Kehr drain was declamped. Interindividual variability ranged from 20 to 70%; there was significant interoccasion variability for several parameters, even when the drain effect was taken into account, reflected in the large diversity of PK profiles.

Conclusions: This study confirms the difficulty of dose adjustment of MMF, due to the large variability of MPA/MPAG concentrations both between and within subjects, especially in these patients with possible renal and hepatic impairment receiving several co-medications. Although we could identify the enterohepatic cycle, its low contribution to overall exposure suggests a simpler PK model can be used for drug adjustment.

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Paul Matthias Diderichsen III-54 Dose selection of GLPG0634, a selective JAK1 inhibitor, for rheumatoid arthritis Phase 2B studies: PK/PD modeling of pSTAT1 biomarker and DAS28 clinical response

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Objectives: GLPG0634 is an orally-available, selective (JAK1) inhibitor and has shown encouraging pharmacodynamics, safety and efficacy in early clinical studies treating RA patients for 4 weeks. The purpose of analysis was to support GLPG0634 dose selection for Phase 2b studies in RA.

Methods: Non-linear mixed effects models were built for plasma pharmacokinetics (PK) of both GLPG0634 and its main metabolite , for the pSTAT1 response in healthy subjects (biomarker) and DAS28 improvement from baseline in RA patients treated for 4 weeks (clinical response). Model-predicted responses for both steady-state pSTAT1 and DAS28 (12 weeks) as well as the contribution of the active metabolite to the biomarker response were investigated for a GLPG0634 dose range of 30-300 mg/day.

Results: The PK of GLPG0634 and its active metabolite were adequately described by an integrated model with two- and one-compartmental disposition, respectively. The observed pSTAT1 response was described by a sigmoidal E_{MAX}. The steady state inhibition of pSTAT1 was predicted to be between 64.3% (pre-dose) and 91.9% (at C_{max}) following treatment with 200 mg GLPG0634 QD with no relevant increase in PD response at higher doses. Simulations indicated that while inhibition is maximal at the peak of GLPG0634, the sustained metabolite exposure results in a continued basal inhibition when GLPG0634 exposure declines. The observed DAS28 change from baseline was adequately described by an indirect response model using the metabolite exposure as a predictor of response. The DAS28 change from baseline was predicted to be -2.2 and -2.6 at week 4 and 12 following 200 mg GLPG0634 QD with no substantial improvement in DAS28 response at higher doses.

Conclusions: This analysis of early clinical data suggests that (1) the pharmacokinetics of GLPG0634 is dose proportional at doses up to 200 mg QD, (2) both GLPG0634 and its main metabolite contribute to pSTAT1 biomarker response, and (3) clinical efficacy (DAS28) increases with the dose up to a daily dose of 200 mg GLPG0634, with clinical response in the range of that observed with JAK inhibitors.

Andre Schäftlein IV-04 Population modeling of the relationship between the pharmacokinetics of the oral thrombin inhibitor dabigatran etexilate and coagulation biomarkers in patients with non-valvular atrial fibrillation from the RE-LY trial

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Objectives: To develop population models describing the relationships between total dabigatran plasma concentrations and the Ecarin clotting time (ECT) as well as the Thrombin time (TT).

Methods: 27399 (ECT) and 8066 (TT) biomarker observation each with an associated dabigatran concentration from 9473 (ECT) and 2173 (TT) patients in the RE-LY trial [1] were included for data analysis in NONMEM 7.2. Time-dependent and independent linear as well as maximum effect (Emax) models were compared based on the results of the Likelihood-ratio test and graphical diagnostics. A covariate analysis was performed using a stepwise forward inclusion (p=0.05) and backward elimination (p=0.001) procedure. Data from two thirds of the patients were used for model development. The remaining observations were used evaluating the predictive performance of the final covariate models.

Results: Time-dependent models were not superior to time-independent models for both biomarkers. Hence, no delayed effect of dabigatran concentration on the coagulation pathway could be detected. A baseline dependent linear model for ECT as well as a combination of a baseline dependent linear and an E_{max} model for TT described the data best. Interindividual variability as well as intraindividual variability on model parameters was moderate for TT (< 37 %CV) and low for ECT (< 15 %CV). The concentration-ECT and concentration-TT relationships were statistically significant affected by sex and age (ECT), and by weight (TT) on the slope, respectively. Nevertheless, simulations revealed that all statistically significant covariates showed only minor effects on the interaction between dabigatran concentration and the measured biomarkers. Adequate predictive performance was confirmed for all developed models based on predictions for the evaluation set.

Conclusions: Two population models relating the dabigatran concentrations to the coagulation biomarkers ECT and TT were successfully developed. Despite the excellent descriptive and predictive performance of the models, the concentration biomarker relationship of anticoagulant drugs in general is dependent on the anticoagulant assay used [2]. This needs to be taken into account in applying the results from RE-LY to clinical practice.

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Mijeong Son IV-14 Population Pharmacokinetic-Pharmacodynamic modeling of Olemsartan in Healthy Korean Volunteers

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Objectives: This study is to investigate the pharmacokinetics (PK) and blood pressure lowering effect (PD) of olmesartan and to find the related covariates in healthy Korean volunteers.

Methods: A randomized, open label, multiple-dose, crossover, drug-drug interaction study was conducted in 36 healthy male subjects. They received a 20 mg rosuvastatin tablet, a 40 mg olmesartan tablet and both over 3 periods, with each formulation being taken once a day for 7 days, with a 8-day washout period between the formulations. Systolic (SBP) and diastolic blood pressure (DBP) were measured before dosing for day 1 through 6 and 0, 2, 4, 8, 12, 24 hr at steady-state after the last dose. Plasma drug concentration and blood pressure data obtained from mono-administration of olmesartan were sequentially analyzed by a population modeling approach using NONMEM [1].

Results: Olmesartan PK was best described by a two-compartment model with first-order absorption. The estimates (relative standard errors %) of oral clearance, volume of distribution of central and peripheral compartments, intercompartmental clearance and absorption rate constant were 5.06 L/hr (3.5%), 14.6 L (13.5%), 17.3 L (6.9%), 1.97 L/hr (8.3%) and 0.462 h^{-1} (13.9%), respectively. With baseline blood pressure modeled with a circadian rhythm with 24-hr period for SBP and 8-hr period for DBP, olmesartan PD was best described by using a log-linear model consisting of a slope linking plasma concentrations to drug effects. Drug effect was assumed to either directly reduce blood pressure for SBP or indirectly reduce blood pressure by reducing the turnover rate (Kin) for DBP which showed a characteristic of hysteresis. The PD model thus obtained yielded parameter estimates of 121 mmHg (2.1%), 0.41 mmHg (156.8%), 11.6 hr (50.6%) and 2.11 (21.3%) for mesor, amplitude, acrophase and slope, respectively, for SBP, and 55.2 mmHg (8.2%), 23.8 mmHg (29.1%), 6.55 hr (3.4%), 1.32 mmHg*h^{-1} (69.4%) and 0.00197 (11.7%) for mesor, amplitude, acrophase, Kin and slope, respectively, for DBP. No covariate was found significant.

Conclusions: This work reported a population PK/PD model obtained for mono-administration of olmesartan. Further studies will include PK/PD model building for mono-administration of rosuvastatin and co-administration of the two drugs. Combined with these future results, the present result will be used as a basis to examine drug-drug interactions between olmesartan and rosuvastatin in Korean population.

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Elisabet Størset IV-17 Evaluation of dosing strategies to achieve targeted tacrolimus exposure after adult kidney transplantation

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Objectives: We have previously developed a theory-based population pharmacokinetic model for tacrolimus in adult kidney transplant recipients [1]. The aim of this study was to examine the extent of target achievement using (i) standard weight-based dosing, (ii) mechanism-based dosing and (iii) Bayesian dosing.

Methods: Dosing strategies were evaluated by simulating the concentration-time profiles of 1000 subjects during the first five days post-transplant with covariate values sampled from the original dataset. For each subject, dosing strategies were based on (i) total body weight (0.04 mg/kg/12 hours) or (ii) standard population pharmacokinetic parameter values and mechanism-based covariates (fat free mass, *CYP3A5* genotype and prednisolone dose, $p<0.001$). Dosing strategy (iii) was designed to imitate the effect of Bayesian forecasting on prediction of individual parameters by tapering between-subject variability to zero over the first five days without a change in between-occasion variability. The target was set to an average steady-state concentration of 14.2 mcg/L (standardized to a hematocrit of 45 %) [2] with an acceptable range defined as 80-125 % of the target concentration [3]. The percentage of concentrations within this range was calculated for each dosing strategy. Modeling, simulation and Bayesian dosing was performed using NONMEM 7.2.

Results: Total weight-based dosing, mechanism-based dosing and Bayesian dosing led to 32 % (95 % CI 29 % to 35 %), 37 % (95 % CI 34 % to 40 %) and 65 % (95 % CI 62 % to 68 %), respectively, of simulated average steady-state concentrations within the suggested acceptable range.

Conclusions: Mechanism-based dosing is of little additional value to improve target achievement of tacrolimus after kidney transplantation compared with weight-based dosing. Bayesian dosing improves target achievement. However, even with ideal Bayesian dose adaptation, 35% of concentrations were outside the acceptable range. To reduce this percentage, efforts should be directed to reducing the between-occasion variability associated with tacrolimus oral bioavailability.

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Pavan Vajjah IV-32 Exposure-response relationship of certolizumab pegol in psoriatic arthritis patients and comparison of ACR 20/50/70 response rates in the two dosage regimens

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Objectives: To describe the relationship between pharmacokinetics (PK) of certolizumab pegol (CZP) and the time course of ACR 20/50/70 in patients with psoriatic arthritis (PsA). The other objective was to compare the time course and magnitude of effect on ACR 20/50/70 response rates at week 24 given the two dosage regimens.

Methods: Data from a phase 3 study in subjects (n=409) with active and progressive PsA was used for the analysis [1]. Subjects were allocated to the following study treatments in a 1:1:1 ratio: 1. CZP administered subcutaneously (sc) at the dose of CZP 400 mg Q2W at Weeks 0, 2 and 4 followed by CZP 200 mg Q2W sc (starting at Week 6) or 2. CZP 400 mg Q2W at Weeks 0, 2 and 4 followed by CZP 400 mg Q4W sc (starting at Week 8) or 3. Placebo. The CZP plasma-concentration-time data was used to develop a PK model. Secondary PK parameters such as Cmax, Cmin and Cavg were determined using the PK model. A proportional odds model was used to simultaneously analyze the ACR 20/50/70 response rates observed in the study. The individual plasma concentrations, AUC, Cmax, Cmin and Cavg were used as exposure measures.

Simulations were performed to predict the time course and magnitude of the of ACR 20/50/70 response rate of CZP in this patient population, given the two dosage regimens used in the current study, to evaluate whether the difference between dosage regimens, if any, could be detected.

Results: A one compartment disposition, zero-order input into a depot compartment, with subsequent first order absorption to central compartment population PK model adequately characterized the plasma CZP concentration time course. The residual variability took the form of a proportional error model. Body weight and anti-drug antibodies (ADA's) were the identified covariates on CL/F Body weight was also a covariate on V/F. An Emax model on the logit scale provided the best description of the time course of ACR 20/50/70. Cavg was determined to be the best predictor of ACR 20/50/70 response criteria.

The simulations performed using the final model indicated that the both the magnitude and the time course of the predicted ACR 20/50/70 response rates for the two dosage regimens (200 mg Q2W and 400 mg Q4W) were similar.

Conclusions: An exposure response model was developed to simultaneously describe the time course of ACR 20/50/70 response rates in psoriatic arthritis population following sc administration of CZP. The results of simulations indicate that the time course and magnitude of ACR 20/50/70 response rates at week 24 are similar for the two tested dosage regimens

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Franziska Weber IV-45 Evaluation of candidate drugs to induce the redundant gene ABCD2 as an alternative treatment option for X-linked adrenoleukodystrophy

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Objectives: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease with impaired very long-chain fatty acid (VLCFA) metabolism. Mutations in the *ABCD1* gene, encoding a peroxisomal membrane protein (ABCD1), cause this clinically heterogeneous disease. X-ALD can manifest as a rapidly progressive, inflammatory cerebral demyelination (CALD). The only curative therapies are transplantations of allogeneic or genetically corrected autologous hematopoietic stem cells. Thus, alternative therapies are urgently needed. Recently, we demonstrated that monocytes but not lymphocytes are affected in X-ALD, implying that metabolic correction of monocytes/macrophages (MO/MP) should halt the inflammation in CALD (1). As overexpression of ABCD2, the closest homologue of ABCD1, restores VLCFA metabolism *in vitro* (2) and *in vivo* (3), we investigated candidate drugs (e.g. retinoids) to induce *ABCD2* in MO/MP.

Methods: The monocytic cell line THP-1, human primary MO and *in vitro* differentiated MP were treated with retinoids for 24h, followed by qRT-PCR analysis of ABCD1/2/3 and HPRT (reference gene) mRNA levels. MO, B cells and enriched T cells were isolated from peripheral blood of controls and acne patients before and during retinoid therapy for analysis of ABCD1/2/3 mRNA levels. A linear mixed effect (lme) model was used with the log-transformed mRNA copies as response and two primary covariates, a gene factor (HPRT, ABCD1/2/3) and a population (Acne patients, controls) or treatment (drug exposure) factor. Using the lme function of the nlme R-package (4, 5) with the treatment contrast, we obtained means of ABCD1/2/3 mRNA normalized to HPRT of controls and differences to the population/treatment factor.

Results: In THP-1 cells, 13-*cis*-retinoic acid (13-CRA) revealed the highest, 5-fold increase (E_{max}) of ABCD2 mRNA with a potency (EC_{50}) of 0.03 µM. ABCD2 mRNA levels in MO of untreated and 13-CRA-treated (0.75 mg/kg over 6 months) acne patients remained in the range of control MO. In differentiated MP treated *in vitro*, we observed a 4-fold induction of the ABCD2 mRNA with 7 µM 13-CRA.

Conclusions: Apparently, the accessibility of the ABCD2 promoter changes during differentiation of MO into MP. However, the relative induction of ABCD2 expression by 13-CRA alone would not suffice to compensate for ABCD1 deficiency in these cells. Lme with the treatment contrast was an effective tool to analyse these data, as the results directly reflect the mean log ratio of ABCD1/2/3 to HPRT.

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Pawel Wiczling IV-48 PK/PD of propofol and fentanyl in patients undergoing abdominal aortic surgery - the influence of cardiac output and drug interactions

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Objectives: Pharmacokinetic (PK) and pharmacodynamic (PD) data of propofol and fentanyl, the cardiac output (CO) measurements, and the bispectral index (BIS) were available from a study of ASA physical status III patients scheduled for abdominal aortic surgery. The aim of the work was to assess the influence of cardiac output on propofol and fentanyl PK/PD and to determine the effect of fentanyl on hypnotic effects of propofol.

Methods: After institutional approval, the data was obtained from ten patients of 50 to 75 years age and weighing between 50 and 92 kg. Propofol was administered by means of the target-controlled infusion system (Diprifusor) and fentanyl was given whenever inadequate analgesia was assessed throughout the surgery at a dose of 2–3 μg/kg. Hemodynamic measurements were done with FloTrac/Vigileo TM (Edwards, USA). The bispectral index (BIS) served to monitor the depth of anesthesia and was kept between 40 and 60. PK/PD analysis was performed by using a non-linear mixed-effect population model (NONMEM 7.2 software).

Results: A three and a two compartment model was sufficient to describe propofol and fentanyl PK. The delay of the anesthetic effect, with respect to plasma concentrations, was described by the effect compartment. The BIS index was linked to the propofol and fentanyl effect site concentrations through a synergistic E_{max} model. In this study the cardiac output has been identified as significant covariant influencing fentanyl disposition (elimination and distribution clearance). The effects of CO on propofol PK were less evident and could not be supported by the present data.

Conclusions: The population PK/PD model was successfully developed to describe the time course and variability of propofol and fentanyl concentrations and BIS index. The effects of CO on fentanyl PK and interactions between fentanyl and propofol were observed in the study.

Eva Germovsek I-13 Mechanistic Modelling of Total Body CD4 T-cell Counts from Paediatric HIV Patients Undergoing Planned Treatment Interruption

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Objectives: Paediatric T-cell population dynamics are influenced by higher thymic output and peripheral T-cell division rates than in adults. CD4 T-cell numbers decline in untreated HIV infection; this can be prevented with antiretroviral therapy (ART), but paediatric patients sometimes interrupt ART. To describe CD4 cell dynamics different complex mechanistic models have previously been tested [1]. However, since only 2% of CD4 cells are in the blood, it is difficult to measure and define all the proposed model parameters, which can limit mechanistic interpretation. The aim is to develop a simpler, mechanistic CD4 reconstitution model.

Methods: Naïve CD4 concentrations from the PENTA 11 trial [2] were converted to total body CD4 counts and modelled using NONMEM 7.3 with FOCE-I. The data included 29 and 31 HIV patients on continuous and interrupted treatment, respectively; mean (range) age 10.2 (2.2-19.1) years. 743 naïve CD4 levels were measured. A mechanistic model [3] with 3 estimated parameters (thymic output, loss of naïve CD4 cells due to death and proliferation, and initial naïve CD4 cell count) was adapted and applied to the data. Effects of age on both input and loss of naïve CD4 cells from the naïve T-cell reservoir were included, as well as a competition function that describes the change in loss with changing cell number [4,5]. A drug parameter was introduced as a time-varying binary covariate.

Results: Compared to a simple 1-compartment model, a model that included age-related effects and competition function provided a 19 unit drop in OFV. One of the parameters describing the competition function was fixed. Other parameters (input as a multiple of that in a healthy child [5], loss, initial cell number and effect of ART) were estimated. Final estimates (relative standard error, %) for these parameters were 0.0407 (28.3), 0.491 day^{-1} (38.3), 61000 cells (5.79) and -0.905 (4.50), respectively. Goodness-of-fit plots and VPC suggest that the model fits the data well and there are no major model misspecifications.

Conclusions: A mechanistic model was used to describe CD4 dynamics, with fewer parameters and ODEs than previous models, and might provide more reliable results. Provisional results imply that ART reduced the net loss of naïve CD4 cells to 9% of the value when off therapy. Future work will consider viral load and memory CD4 cells in the model, to further understanding of the effects of treatment interruption on long-term CD4 reconstitution.

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Rollo Hoare I-33 Modelling CD4 lymphocyte reconstitution following paediatric haematopoietic stem cell transplantation

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Objectives: Before a haematopoietic stem cell transplant (HSCT), a child will usually be given a conditioning regimen to reduce or ablate the host immune system. This is to prevent graft rejection, graft versus host disease and relapse. Following HSCT, short-term complications and long-term successful outcomes are associated with the rate and extent of immune system recovery. Studying immune reconstitution in children is challenging due to the rapidly developing immune system; expected CD4 T cell counts (a key subset of lymphocytes) for age decrease three-fold [1]. This work presents an extension of our mechanistic model, describing reconstitution of CD4 cells in children following HSCT, to include a more biological explanation of competition for resources [2].

Methods: The model of CD4 cell count has two compartments, a resting and dividing compartment. Cells enter the resting compartment through a zero-order thymic output. They can then be activated to the dividing compartment from which two cells will return to the resting compartment. There are different death rates for cells in each compartment. The model is made more mechanistic in three ways: (1) using a mathematical function for thymic output [3] to account for age related changes; (2) allowing for impaired thymic output in the months following HSCT; (3) having density dependent death and activation rates to account for competition for resources. We apply this model to longitudinal data collected in the bone marrow transplant unit in Great Ormond Street Hospital.

Results: Fitting this model using NLME has proved difficult due to collinearities. After theoretical and practical identifiability analysis, by selecting density dependencies and parameter sets, it has been possible to find a model that is identifiable. The final model had good descriptive and simulation properties. In the long term, the modelled population average returned to, or very near to, the CD4 count expected for a healthy child.

Conclusions: A mechanistic model for immune reconstitution of CD4 cells following HSCT has been extended to include a more biological explanation for the competition for resources, using two compartments. We manage to fit this model to the data, finding a set of parameters that are identifiable. It is now possible to carry out a multivariate analysis and find which parts of the immune system are affected by covariates such as disease type, drug pre-conditioning, and graft-versus-host disease prophylaxis.

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Esther Janssen I-38 Simulations of vancomycin exposure throughout childhood upon commonly used dosing guidelines: towards a model-based dosing regimen

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Objectives: Despite many reports on the pharmacokinetics of vancomycin in children, target concentrations of vancomycin in daily practice are difficult to reach. Recently, the developmental changes in glomerular filtration (GFR) mediated elimination of gentamycin, tobramycin and vancomycin from neonates to adulthood were characterised [1]. In the present study, the GFR model of vancomycin [1] was used to evaluate vancomycin exposure in children upon commonly used dosing algorithms. Ultimately, a model-based dosing regimen that will lead to predictable exposure across children is derived.

Methods: Concentration-time profiles were simulated using the GFR model of vancomycin [1] in typical children aged 1 month-18 years. Both intermittent and continuous dosing regimens were simulated according to British National Formulary for children, Dutch Children's Formulary, IDSA, National Neonatal Formulary and other publications [2-4]. Target trough concentrations were 10-15 mg/L or 15-20 mg/L after intermittent dosing. For continuous dosing, target concentrations were 15-25 mg/L. In all cases, the concentration should not exceed 40 mg/L.

Results: Children aged <1 year were exposed to a large variety in concentrations for the different intermittent and continuous dosing regimens. For children older than 1 year, vancomycin exposure seems within the target concentration when dosed 60 mg/kg/day. Steady state concentrations were reached between 31 and 53 hours of dosing for children aged >1 year and a 1 month old infant, respectively, suggesting the need for a loading dose in particularly the youngest age ranges.

Conclusions: On the basis of this simulation study, a model-based dosing algorithm is proposed that will result in optimal vancomycin concentrations after either intermittent or continuous dosing for children aged < 1 year. For children aged 1 year or older, a maintenance dose of 60 mg/kg/day seems appropriate. A clinical study is needed to demonstrate the prospective value of this dosing regimen.

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Jean Lavigne II-06 Modeling and simulation of dihydroartemisinin (DHA) after administration of Eurartesim® (piperaquine tetraphosphate/DHA)

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Objectives: Develop a population pharmacokinetic (PK) model for DHA by pooling data from 5 studies and apply it to predict DHA PK in pediatric patients (6 - 12 months) infected with *Plasmodium falciparum* malaria after administration of a new dispersible formulation.

Methods: Subjects/patients with at least one measurable DHA concentration were included in the analysis for a total of 201 DHA profiles, 3460 samples (2340 were measurable). The MLEM algorithm in ADAPT5[1] was used to estimate the population parameters. Concentrations below the limit of quantification were treated as censored. The M3 method from Beal[2] was used. The covariates age, body weight (WGT), body surface area, sex, race, fasted/fed (FED), health status healthy/patient (PAT), formulation old/new (FORM) and crushed/not crushed were explored. The general additive model in R[3] version 3.0.1 was used for covariate selection. The Bayesian Information Criteria (BIC) was used for model discrimination and covariate inclusion/exclusion.

Results: A one-compartment model with lag time and zero-order absorption was the structural model that best fitted the DHA data. Body weight corrected dose improved the BIC. PAT was a significant covariate on Lag, zero-order duration (Tk0), and relative bioavailability (Frel) (on healthy). FED was a significant covariate on Lag and Tk0. FORM was a significant covariate on Frel (on the old formulation). For the simulations, WGT was simulated according to the WHO training[4]. Two thousand infants were simulated (gender balanced) receiving 10, 20, or 40 mg of DHA depending of their WGT once a day for 3 consecutive days. AUC, Cmax and Tmax were calculated. For the new dispersible formulation, the simulated results suggest that the geometric mean of DHA AUC (Dose/Clearance) and Day 3 Cmax should be 1160 ng/mL*h and 407 ng/mL, respectively under fasting condition and 1180 ng/mL*h and 237 ng/mL*h, respectively under fed condition. The median Day 3 Tmax would be 2.5 h and 5.1 h under fasting and fed condition, respectively.

Conclusions: A one-compartment structural model with lag time and zero-order absorption best described the PK of DHA. Body weight, health status, food and formulation were the 4 covariates which improved the model. It is expected that DHA will have similar exposure under fasting and fed conditions. Cmax under fed condition would be about half of that under fasting condition and Tmax should be delayed about 2.6 h under fed relative to fasting condition.

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Olaf Lichtenberger II-13 Evaluation of tetrahydrobiopterin responsiveness in neonates with hyperphenylalaninemia

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Objectives: Hyperphenylalaninemia (HPA) is the most common dysfunction of metabolism of amino acids, caused by a missing or reduced activity of either the enzyme phenylalanine hydroxylase (PAH) or one of four enzymes involved in the tetrahydrobiopterin (BH4) metabolism. Mutations or deficiencies of any of these enzymes may give rise to pathologically increased phenylalanine concentrations, which can lead to intellectual disability, seizures, and other serious medical problems [1,2].

This paper presents a phenylalanine turn-over model in neonates with HPA receiving a BH4 loading test.

Methods: Neonatal phenylalanine concentrations from 375 patients with PAH deficiency and 194 with BH4 synthesis deficiency receiving a BH4 test dose were modeled against time and dose using nonlinear mixed-effect approach (NONMEM). A kinetic pharmacodynamic (KPD) approach was chosen to describe the phenylalanine concentration vs. time, since no PK of BH4 was available. Out of the different types of turn-over model, the closest one to the mechanism of action is the “Stimulation of Loss”, driven by the dose of BH4 delivered to the effect compartment. Inter-individual variability terms on KDE (the elimination of BH4 concentration from effect compartment), Kout (loss from phenylalanine compartment) and on slope effect parameters have been considered.

A mixture population approach, with 2 different populations has been used in order to differentiate response (Re) from non-response (NRe). In the model the slope parameter of NRe was set to zero, whereas the slope of Re was estimated, according to the sub-population estimated by NONMEM.

Results: The KPD turnover model describes appropriately the phenylalanine concentration vs. time. Using the model we found that 193 out of 194 patients with deficiency of BH4 synthesis are responders. In contrast, among patients with PAH deficiency, 42.4 % are estimated to be non-responders.

Diagnostic plots show that the model fits the data well, with good precision and without bias. The mixture model differentiation between Re and NRe was externally qualified by comparing the responsiveness with a 48-h based prognostic test [3].

Conclusions: The KPD model “Stimulation of Loss” coupled with mixture model for classification between Re and NRe allows a more objective description of the BH4 effect than previous analyses and could facilitate further correlation studies investigating various demographic, laboratory, and genetic parameters.

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Merran Macpherson II-17 PPK analysis of Rouvastatin in Children and Adolescents (ages 6 to

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Objectives: To describe the pharmacokinetic properties of rosuvastatin in children ≥6 to < 18 years of age.

Methods: A two-compartment population model was fitted to a total of 2029 measurable rosuvastatin concentrations from 214 patients using NONMEM 7.2.0. Covariates were evaluated against CL/F by a stepwise forward inclusion (α = 0.01) and backward exclusion (α = 0.001) process to the base model. The final model was evaluated using a VPC, stratified by sampling intensity (intense/sparse), dose and study. The dose equivalent exposure range in healthy adults and patients was graphically compared to children and adolescents with hypercholesterolaemia.

Results: A linear two-compartment disposition model with a 1st order absorption and elimination processes (ADVAN4 TRANS4) adequately described the combined dataset. Dose and time did not significantly affect CL/F within the studied dose and treatment period. Weight and gender were found to be significant covariates for CL/F and remaining between patient variability was moderate (CV 40 %). Age could not significantly explain any additional variability in CL/F. CL/F increased with increasing weight and represented a 2-fold difference (max/min) across the observed weight range and CL/F in female children was approximately 30% lower than in male children. Pharmacokinetics of rosuvastatin in children and adolescents with FH is more similar to healthy adults than adult patients with dyslipidaemia.

Conclusions: The pharmacokinetics of rosuvastatin in children and adolescents with HeFH was adequately described by the population PK model and appears to be predictable with respect to both dose and time. Children with lower body weights had on average lower clearances but it is unlikely that this covariate (as well as gender and age) has a relevant impact on steady state exposure because the youngest children (>6 years to Tanner less than II) are prescribed a maximum dose of 10 mg whereas older children and adolescents can receive up to 20 mg.

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Andreas Matthios II-20 Dosing recommendation for gabapentin in chronic paediatric pain

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Objectives: The main objective of this analysis is to identify an exposure range for gabapentin that can be used as target for subsequent dosing recommendation in children between 3 months and 12 years old. In addition to defining the dose rationale, optimal design principles are used that allow efficient pharmacokinetic sampling in a prospective clinical trial in the paediatric population.

Methods:A nonlinear mixed effects model was developed using NONMEM v.7.2. Exposure simulations and parameter re-estimation were evaluated using a one compartment pharmacokinetic model with IIV in CL and Vd and renal function and body weight as covariates on drug disposition parameters. R was used for data analysis manipulation and graphical purposes.

Results: Covariate distribution was estimated by using literature data. The target exposure of the starting and maximum doses was estimated to be between 50 and 187 (µg.h/mL) respectively. Scenarios taking into account the role of body weight and renal function were performed to explore the starting dose and titration schedule in the paediatric population.

Conclusions: The Schwartz formula was found to efficiently replace the Cockcroft formula to describe the effects of maturation and growth on renal function in children. Moreover, our results show that the population pharmacokinetic model may be used for extrapolation purposes in children. A titration scheme is proposed to mitigate the adverse events known to occur at onset of treatment

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Johanna Melin II-21 Population pharmacokinetic analysis of hydrocortisone in paediatric patients with adrenal insufficiency

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Objectives: Patients with congenital adrenal hyperplasia (CAH) have an impaired synthesis of cortisol, leading to accumulation of cortisol precursors and elevated concentrations of androgens. Substitution therapy with glucocorticoids, especially in growing children, is important but challenging to optimise: Too high exposure to glucocorticoids may increase the risk of reducing final-height and development of Cushing's syndrome, whereas too low exposure may increase the risk for Addisonian crisis and disease progression [1]. Dosing decisions are currently based on body weight or body surface area (BSA), and clinical signs of adrenal suppression. The objective of this study was to gain prior knowledge for an upcoming PK study in a new paediatric population, by characterising the pharmacokinetics of hydrocortisone (i.e., synthetic cortisol) in paediatric patients with CAH.

Methods: For model development, patients included in the study were 7-18 years old and diagnosed with CAH. Cortisol concentrations over 6 h were available after single intravenous (i.v.) administration of hydrocortisone succinate and cortisol concentrations over 24 hours after twice or thrice daily oral administration of hydrocortisone [2][3]. The i.v. dose was individualised based on BSA (dose range: 14.2 - 30.2 mg), and regular oral therapeutic regimens were administered twice or thrice daily (dose range: 2.5 – 20 mg). Population pharmacokinetic analysis was performed using NONMEM 7.3. Precision of parameter estimates was assessed by performing bootstraps.

Results: Concentrations from 16 patients after i.v. and from 30 patients after oral administration were used for model development. A one compartment model with first-order absorption and elimination successfully described the data under the different studied dosing regimens. The estimated parameters were in agreement with literature data [1][3][4], except for the bioavailability, which was lower (77.6 %). Interindividual variability was implemented in absorption rate constant, clearance, volume of distribution and bioavailability.

Conclusions: A population pharmacokinetic analysis for hydrocortisone in paediatric patients with congenital adrenal hyperplasia has successfully been developed. The model is intended to be used for establishing an optimal design for a study in patients younger than six years, and for optimising the hydrocortisone therapy in this patient group.

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Hussain Mulla II-30 Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration.

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Objectives: Since glomerular filtration rate (GFR) is responsible for the elimination of a large number of water-soluble drugs [1], the aim of this study was to develop a semi-physiological function for GFR maturation from neonates to adults.

Methods: In the pharmacokinetic analysis (NONMEM VI) based on data of gentamicin, tobramycin and vancomycin collected in 1760 patients (age 1 day-18 years, bodyweight 415g-85kg), a distinction was made between drug-specific and system-specific information. Since the maturational model for clearance is considered to contain system-specific information on the developmental changes in GFR [2], one GFR maturational function was derived for all three drugs.

Results: Simultaneous analysis of these three drugs showed that maturation of GFR mediated clearance from preterm neonates to adults was best described by a bodyweight-dependent exponent (BDE) function with an exponent varying from 1.4 in neonates to 1.0 in adults ($Cl_{GFR}= Cl_{drug}*(BW/4kg)^{BDE}$ with $BDE=2.23*BW^{-0.065}$). Population clearance values (Cl_{drug}) for gentamicin, tobramycin and vancomycin were 0.21L/h, 0.28L/h and 0.39L/h for a full term neonate of 4kg, respectively.

Conclusions: Based on an integrated analysis of gentamicin, tobramycin and vancomycin, a semi-physiological function for GFR mediated clearance was derived that can potentially be used to establish evidence based dosing regimens of renally excreted drugs in children.

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Flora Musuamba-Tshinanu II-32 Optimisation of tacrolimus-based immunosuppressive treatment in pediatric solid organ transplantation: A model-based approach.

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Background: Tacrolimus is considered to be the mainstone of immunosuppressive therapy after solid organ transplantation. However, if its efficacy is now well established, the nephrotoxicity associated with its long-term use is currently the biggest challenge in the short term and long term outcome of pediatric and adult transplantation. Tacrolimus optimal dosing is therefore still challenging: tacrolimus dose is most frequently tailored either based on patient characteristics or based on monitored concentrations.

Objectives: The objective of this study is to characterise the relationships between the dose, the concentrations and the clinical effects but also target exposure levels for tacrolimus in pediatrics.

Methods: A physiologically based pharmacokinetic (PBPK) model was first developed for tacrolimus and was used to fit adult and pediatric patient data in different types of solid organ transplantations. Subsequently a pharmacokinetic-pharmacodynamic (PK/PD) model was developed to characterise the relationship between tacrolimus exposure, pharmacodynamic biomarkers (lymphocytes, leucocytes, interleukines, cytokines, etc) and clinical outcome (graft rejection and nephrotoxicity).

Results: The developed PBPK model displayed good fitting performances for pediatric and adult data and was used to predict tacrolimus exposure levels for subsequent PK/PD model development. Indirect exposure-response models were developed for the PD biomarkers whereas a time to event model was used to predict the clinical outcome based on the predicted biomarker levels.

Conclusion: The developed models constitute a first step toward a better characterisation of the target exposure for tacrolimus in pediatric patients. The developed model should be externally and prospectively validated before its implementation in clinical practice.

Sophie Peigne II-46 Paediatric PK predictions and population analysis

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Introduction: The "first dose in children" can be determined by either Physiollogically based PharmacoKinetics model (PBPK) or compartmental approach using allometric scaling and maturation functions [1]. These methods were applied in a study conducted in paediatric population with drug S (currently marketed in adult population), 80 % metabolized via CYP3A4 and for about 20 % renally eliminated by glomerular renal filtration (GFR).

Objective: The aim of this work was to provide an example of paediatric dose prediction using the two later approaches. Another objective was to analyse the data of the paediatric study.

Methodology: A clinical study was conducted in paediatric patients treated during one year and aged 6 months to 18 years old. For each patient, 5 blood samples were collected at steady state in order to measure the parent drug S and its main active metabolite. Before PK analysis, through a simulation approach, those observed data were compared with PK children predictions using:

- a full PBPK model developed with SimCyp and
- an adult semi- physiologic joint PK model for the drug S and its active metabolite scaled to children with weight effects fixed to the allometric values of 0.75 and 1 on clearances and volumes of distribution, respectively [2]. In addition, for the youngest age classes, a maturation function was added on first past effect and intrinsic clearances to reflect CYP3A4 maturation [3] and on renal clearances to reflect GFR maturation [4].

The best approach was selected regarding overall numerical predictive check (NPC). The sparse PK data were then analyzed using a compartmental population PK approach. The model was evaluated with NPDE.

Results: For the parent drug, the concentrations predicted by SimCyp were slightly higher than the simulated concentration time profiles obtained by compartmental population approach, especially for the youngest age class (6-12 months). Overall, the inter-individual variability was slightly higher with the compartmental approach [5]. A compartmental analysis on paediatric PK data led to a joint parent-metabolite model which described adequately the data.

Conclusion: The approaches were compared and showed slightly higher predictions especially in the absorption phase for the parent drug. These differences were more pronounced with the youngest age class. In a next step, PKPD simulations will be performed for dose selection based on the clinical target PD effect.

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Yulan Qi II-51 A Prospective Population Pharmacokinetic (PK) Analysis of Sapropterin Dihydrochloride in Infants and Young Children with Phenylketonuria (PKU)

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Objectives: To determine the appropriate dose of sapropterin dihydrochloride, a synthetic preparation of naturally occurring phenylalanine hydroxylase (PAH) cofactor tetrahydrobiopterin (BH4), in pediatric patients (0-6 years) with PKU, a hereditary metabolic disorder caused by a PAH mutation [1,2,3].

Methods: The study design used D-optimization based on a previous model and was prospectively powered to achieve precise estimates of clearance (CL/F) and volume of distribution (V/F) in each age group [4,5]. A series of structural models were evaluated, including 1- and 2-compartment models with 1st-order input, with and without an absorption lag. Decision making during model building was guided by evaluation of change in objective function, magnitude of inter-individual and residual variability, and diagnostic plots. The model was tested and qualified by evaluating precision of the final parameter estimates, evaluating the condition number, and determining both symmetrical 95% confidence intervals (CIs) from asymptotic standard errors of the parameter estimates, as well as stratified non-parametrically bootstrapped 95% CI. Standard diagnostic plots and visual and numerical predictive checks were evaluated. The power to evaluate CL/F and V/F was evaluated using the final model and database to confirm the prospective evaluation. The analysis was performed with NONMEM version 7.2 on pooled data from 114 pediatric and 42 adult PKU patients in 2 phase 3 clinical studies. Oral sapropterin was administered once daily. Sapropterin plasma concentration was measured by a validated LC/MS/MS method.

Results: The best PK model was a 1-compartment model with an absorption lag and 1st order input and 1st order elimination, with a factor describing endogenous BH4 levels. Body weight was the only covariate significantly affecting sapropterin PK. Model evaluations suggested the model was appropriate. Based on recommended weight-based dosing, exposure across age groups was comparable. The absorption half-life of 2.95 hours and elimination half-life of 0.78 hours suggest flip-flop PK behavior in which absorption is rate limiting.

Conclusions: The effect of weight on sapropterin PK was substantial and dose regimens based on weight are appropriate. Overall exposure across all age groups is comparable. Given the absorption and elimination half-life, once daily dosing is justified.

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Rick Admiraal III-03 Population pharmacokinetic modeling of Thymoglobulin in children receiving allogeneic-hematopoietic cell transplantation (HCT): towards individualized dosing to improve survival

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Objectives: To prevent graft versus host disease (GvHD) and rejection in hematopoietic cell transplantation (HCT), children receive anti-thymocyte globulin (ATG), a polyclonal antibody depleting T-cells, as part of the conditioning regimen. The therapeutic window is critical as over-exposure may result in delayed reconstitution of donor T-cells and increased risk of viral infections. Our objective is to describe the population pharmacokinetics (PK) of Thymoglobulin as a first step towards an evidence based dosing regimen of Thymoglobulin for HCT in children.

Methods: PK data were collected for all pediatric HCT's performed between 2004-2012 in two study centers in the Netherlands. Serum active Thymoglobulin concentrations were quantified by flow cytometry investigating the binding to a T-cell line. Since reference concentration were measured as fluorescent intensity per mg of ATG, active ATG is measured in arbitrary units (AU). Population modeling and covariate analysis was performed on active Thymoglobulin concentrations using NONMEM 7.2. The model was validated using bootstrap and NPDE.

Results: A total of 280 HCT's in 267 patients were analyzed. A two-compartment model with saturable distribution towards the peripheral compartment (described with maximum rate Tmax and Michaelis Menten constant Tm, shown as population mean (RSE), are 155 AU/day (13.7%) and 7.1 AU/L (16.9%) respectively), as well as a parallel linear clearance (Cl; 2.1 L/day (5.7%)) and saturable clearance (described with Vmax and Km, 1.7 AU/day (18.8%) and 1.1 AU/L (21.4%) respectively), yielded a good description of the data in all age groups. The central volume of distribution (V1) was 7.9 L (5.4%), with a K21 of 1.3 day^{-1} (18.6%). The relationship between bodyweight and both Cl and V1 was best described by a power function with an exponent of 0.78 (10.8%) and 1.15 (6.9%), respectively. Cl was influenced by baseline lymphocyte count, with an increase of $1*10^9$ lymphocytes leading to a 30% (18.9%) increase in Cl. Results of the validation steps were satisfactory.

Conclusion: In the validated population PK model for active Thymoglobulin in children, Cl and V1 proved dependent on body weight in a nonlinear manner, while baseline lymphocytes were linearly influencing Cl. Simulations show the current dosing regimen with a cumulative dose of 10 mg/kg over 4 days to be suboptimal, with higher bodyweight children having higher exposures when compared to low bodyweight children.

Elisa Calvier III-29 Use of semi-physiological covariate model for maturation of glucuronidation to scale from adults to children

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Objectives: A semi-physiological covariate model describing the glucuronidation clearance (Clgluc) of morphine in young children was successfully applied to model zidovudine paediatric pharmacokinetic data [1]. As both drugs are mainly metabolized by UGT2B7 and have a high unbound drug fraction (fu) and extraction ratio (ER), a simulation study was undertaken in which it was found that physicochemical drug properties did not influence this covariate relationship [2]. More recently, using a bodyweight-dependent exponent model, this covariate model has been extended to adults [3] and thus could potentially be used to predict paediatric Clgluc based on body weight (BW) only. The objective of this study was to assess the predictive value of the recent semi-physiological covariate model (SPC) [3] compared to classical allometric scaling (CAS) for scaling Clgluc from adults to different paediatric ages for drugs metabolized by UGT2B7 or UGT2B15 and with different fu and ER.

Methods: Literature values for CLgluc in adults for zidovudine (high fu, high ER) [4], lorazepam (low fu, low ER) [5], both metabolized by UGT2B7, and paracetamol (high fu, low ER, glucuronidated by UGT2B15) [6] were scaled by SPC [3] and by CAS (with a fixed exponent of 0.75) to predict CLgluc across the paediatric weight-range. The predictions were compared to values of population glucuronidation clearance in children [1][5][7][8][9][10] with the use of 3-fold prediction interval, bias (mpe or mean percentage error) and precision (rmse or root mean-squared error). For the predictions, 60 to 75%, 100% and 50 to 60% glucuronidation was assumed in adults for zidovudine, lorazepam and paracetamol respectively. For zidovudine and lorazepam, CLgluc was directly extracted from literature on iv administration. For paracetamol, CLgluc was derived from urine collection data on at least 24h. Age-based covariates and age ranges of the PK studies were converted into corresponding median BW according to WHO growth charts.

Results: For neonates the predictions from SPC are significantly less biased (>10 fold) than those from CAS. For infants, the bias of SPC predictions are either close to (lorazepam) or 100 fold less (paracetamol) than with CAS. For children and adolescents, similar trends can be observed. Apart from adolescents, SPC predictions are systematically more precise than CAS predictions. Observations for neonates are at least partially (zidovudine and paracetamol) or entirely (lorazepam) in the 3-fold prediction interval of the SPC and either partially (zidovudine) or completely (lorazepam and paracetamol) out of the 3-fold prediction interval of the CAS predictions.

Conclusions: Scaling drug clearance from adults to children using a semi-physiological covariate model is a rapid and accurate approach that requires less information than whole-body PBPK modelling and should be preferred over the classical allometric scaling approach.

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Stephan Schmidt IV-07 Evaluation of changes in oral drug absorption in preterm neonates for BCS class I and II compounds

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Objectives: Evidence suggests that the rate of oral drug absorption changes from birth, yet, the clinical implications are currently unclear, in particular for preterm neonates. The objective of this study was to: *i*) better understand and quantify changes in oral drug absorption for different Biopharmaceutics Classification System (BCS) class I and II compounds and *ii*) to provide a rational dosing guide for orally administered drug formulations.

Methods: Following a thorough literature search, two paradigm compounds were selected from BCS class I (acetaminophen (APAP) [1, 2] & theophylline [3, 4]) and II (indomethacin [5, 6, 7, 8] & ibuprofen [9, 10]), respectively, based on the availability of clinical data following intravenous (IV) and oral dosing. A population pharmacokinetic (PopPK) analysis was performed in a step-wise fashion in NONMEM® 7.2 to characterize and predict changes in oral drug absorption from birth. Maturational changes in systemic clearance were evaluated based on IV data followed by a BCS class-specific evaluation of changes in pre-systemic events following oral dosing. Due to a lack of published PopPK study data on ibuprofen, the rate and extent of oral drug absorption for ibuprofen in preterm neonates was characterized based on published PK data.

Results: A one-compartment model with an age-dependent maturation function for the rate of absorption was found appropriate to characterize the pharmacokinetic (PK) of APAP. The maturation function for APAP was also sufficient to characterize the PK of theophylline following oral dosing in preterm neonates indicating that the underlying physiological process are drug-independent and the determined maturation function might be generally applicable. Once in solution, indomethacin, a BCS class II compound, showed a similar absorption profile as the two BCS class I compounds suggesting that the use of the maturation function can even be expanded to BCS class II compounds. Our findings further suggest that the rate of drug absorption reaches adult levels within approximately 1 week from birth and that there is a pronounced food effect which contributes to substantial between-subject variability in drug exposure.

Conclusions: For BCS class I and II drugs, age dependent changes in the rate of oral drug absorption appear to drug-independent. A respective maturation function can be applied across these drugs once solubility-related limitations are addressed via appropriate drug formulations.

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Pyry Välitalo IV-34 Evaluation of gentamicin and tobramycin dosing guidelines for neonates; towards model-based dosing

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Objectives: Recently, a neonatal pharmacokinetic model for amikacin has been published upon which a novel model-based dosing regimen was proposed [1]. As the amikacin covariate model was able to predict clearance of other renally cleared antibiotics such as gentamicin and tobramycin [2], the purpose of this study was to evaluate the performance of currently used gentamicin and tobramycin dosing guidelines for neonates in terms of achievement of recommended peak (5-12mg/L) and trough (<0.5mg/L) concentrations.

Methods: The recently published pharmacokinetic model for gentamicin and tobramycin [2] was used for deterministic and Monte Carlo simulations in neonates treated up to one week using NONMEM VII. The performance of existing dosing guidelines (the Dutch Children's Formulary, the British National Formulary for Children, the Red Book, Neofax and Neonatal Formulary) was evaluated. Furthermore, a new dosing protocol was proposed.

Results: In the deterministic simulations with representative patients, most dosing guidelines resulted in trough concentrations above 0.5mg/L which is associated with increased renal toxicity. Monte Carlo simulations of existing dosing guidelines showed gentamicin peak and trough concentrations exceeding the recommended range more often than tobramycin concentrations. For the model-based dosing guideline, a uniform weight-scaled dose was found to lead to optimal peak concentrations, while the dosing interval to reach target trough concentrations was determined based on postnatal age and birth bodyweight.

Conclusions: Existing neonatal dosing guidelines for gentamicin and tobramycin are suboptimal across the heterogeneous population of preterm and term neonates. The proposed dosing guideline, which is based on birth bodyweight and postnatal age, performs well in terms of achieving the target concentrations.

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Anne van Rongen IV-38 Population pharmacokinetics of a single intravenous dose of midazolam in obese, overweight and non-obese adolescents

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Objectives: Midazolam is a commonly used CYP3A4 metabolized benzodiazepine for preoperative sedation in pediatric anesthesia. Although there are numerous studies investigating the pharmacokinetic (PK) properties of midazolam in children with normal weight, no data are available in overweight and obese children. The aim of this study is to determine the pharmacokinetics of midazolam in obese, overweight and non-obese adolescents.

Methods: Nineteen overweight (BMI percentile between 85th and 94th) and obese (BMI percentile > 95th) patients with a mean body weight of 102.7 kg (62 - 149.8 kg), mean BMI of 36.1 kg/m2 (24.8 - 55 kg/m^2) and a mean age of 15.9 years (range 12.5 - 18.9) and 1 non-obese patient (63 kg, BMI 21.2 kg/m^2, 15.2 years) participated in the study. All patients received 2 or 3 mg intravenous midazolam as pre-operative sedative drug. Blood samples were drawn at 0 (pre-dose), (5), 15 and 30 minutes and 1, 2, 4, 6 and (8) hours post dose. Midazolam and its metabolites were determined using HPLC-tandem MS. In addition, data were available of 5 non-obese patients with a mean body weight of 48.0 kg (range 36.4-60.1 kg) and mean age of 14.9 years (range 12.1-16.2 years) [1]. Population PK and covariate modelling was performed using NONMEM 7.2.

Results: A two compartment pharmacokinetic model best described the data for midazolam in obese, overweight and non-obese adolescents. The covariate analyses identified total body weight as covariate for clearance and peripheral volume of distribution with population values of CL_{MDZ} (L/min) = 0.57+ 0.00718*(WT-88.6) and $V_{peripheral}$ (L) = 66.5*(WT/88.6)$^{2.67}$ respectively. Based on the individual patients in the study, this yielded in individual clearances between 0.20 and 1.01 L/min and individual peripheral volume of distribution between 6.2 and 270.2 L. No other covariates could be identified for central volume of distribution or intercompartmental clearance.

Conclusions: In this study, an important influence of total body weight was found on clearance and peripheral volume of distribution in obese, overweight and non-obese adolescents. Further analysis on the basis of a model which distinguishes between bodyweight related to growth and bodyweight related to obesity [2] is needed to further explore the impact of different degrees of obesity in adolescents.

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Chenguang Wang IV-43 Population pharmacokinetics of paracetamol across the human age-range from (pre)term neonates, infants, children to adults

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Objectives: In order to characterize the variation in pharmacokinetics of paracetamol across the human age span, we performed a population pharmacokinetic analysis from preterm neonates to adults with specific focus on clearance.

Methods: Concentration-time data obtained in 220 neonates (post-natal age 1-76 days, gestational age 27-42 weeks) [1,2,3], infants (0.11-1.33 years) [4,5], children (2-7 years) [6] and adults (19-34 years) [7,8] were analysed using NONMEM 7.2. In the covariate analysis, linear functions, power functions, and a power function with a bodyweight-dependent exponent [9] were tested.

Results: Between preterm neonates and adults, linear bodyweight functions were identified for Q2, Q3, V1, V2, and V3, while for CL a power function with a bodyweight-dependent exponent k was identified ($CL_i=(BW_i/70)^k$).The exponent k was found to decrease in a sigmoidal manner with bodyweight from 1.2 to 0.75, with half the decrease in exponent reached at 12.2kg. No other covariates such as age were identified.

Conclusions: A pharmacokinetic model for paracetamol characterizing changes in pharmacokinetic parameters across the entire human lifespan (preterm and term neonates, infants, children, and adults) was developed in which CL was found to change in a non-linear manner with bodyweight. The results may provide insight in the exact relation between weight and CL and as such provide a guide for individualized dosing in children. Once the therapeutic target concentration is known, corresponding appropriate doses can be easily calculated based on this model.

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Morris Muliaditan IV-58 Population Pharmacokinetic Meta-Analysis of the Antiretroviral Agent Lamivudine in HIV-Infected Children

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Objectives: Lamivudine (3TC), a key nucleoside reverse transcriptase inhibitor (NRTI) against human immunodeficiency virus (HIV), is currently approved for twice daily administration in HIV-infected children of at least 3 months. A model-based approach was applied during the course of drug development and post-approval [1] to obtain a deeper understanding of the oral pharmacokinetic properties of 3TC in children. Given the availability of additional oral and intravenous paediatric PK data, a meta-analysis was performed with the objective of validating and refining the previously published PK model [1].

Methods: 3TC concentration-time data from 209 paediatric HIV-infected patients enrolled in six clinical trials were included in the population PK analysis. Parameters were first estimated using data from the three initially available studies to confirm consistency of the structural model and covariate effects with a previously published PK model [1]. This initial model was subsequently used to predict 3TC PK in three external studies followed by a meta-analysis of all available studies for model refinement. Model performance was based on secondary PK parameters ($AUC_{0\text{-}24h}$, C_{max} and C_{τ}). The analysis was performed using a non-linear mixed effect approach, as implemented in NONMEM 7.0.

Results: The pharmacokinetics of 3TC following oral administration were well-described by a one-compartment model with first order absorption and elimination, as published earlier [1]. Weight was a significant covariate on CL and V. Absolute bioavailability (F1) for tablet and solution was introduced in the PK model to account for differences between formulations. The predictive ability of the model was confirmed and diagnostic plots showed good agreement of predicted and observed secondary PK parameters.

Conclusion: Our analysis provided a robust set of parameters to describe the population PK of 3TC, which can be used to evaluate prospective study design, dosing regimens and covariate effects in children. The analysis also confirms the suitability of the model to inform the potential of a once daily dosing regimen in children of at least 3 months of age, as currently prescribed in adults.

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Oscar Della Pasqua IV-59 Population Pharmacokinetic Meta-Analysis of the Antiretroviral Agent Abacavir in HIV-Infected Children

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Objectives: Abacavir (ABC) is one of the recommended nucleoside reverse transcriptase inhibitor (NRTI) against human immunodeficiency virus (HIV); ABC is presently approved for twice daily administration in HIV-infected children of at least 3 months. A model-based approach has been applied during the course of drug development and post-approval to obtain a deeper understanding of the oral pharmacokinetic properties of ABC in children [1]. Given the availability of additional paediatric PK data, a meta-analysis was performed with the objective of validating and refining the previously published PK model [1].

Methods: ABC concentration-time data from 169 paediatric HIV-infected patients enrolled in six clinical trials were included in the population PK analysis. Parameters were first re-estimated using data from the three initially available studies to confirm consistency of the structural model and covariate effects with previously published PK models [1]. This model was subsequently used to predict ABC PK in three external studies followed by a meta-analysis of all available studies for model refinement. Model performance was based on secondary PK parameters ($AUC_{0\text{-}24h}$, C_{max} and C_{τ}). The analysis was performed using a non-linear mixed effect approach, as implemented in NONMEM 7.0.

Results: The pharmacokinetics of ABC following oral administration were well-described by a 2-compartmental model with first order absorption and elimination, as published earlier [1]. Weight was a significant covariate on CL/F and V/F. A study-specific relative bioavailability term (F1) for tablet and solution was introduced in the PK model to describe substantially higher observed exposure in ARROW Substudy Part 2 compared to other studies despite administration of similar doses/formulations. The predictive ability of the model was confirmed and diagnostic plots showed good agreement of predicted and observed secondary PK parameters.

Conclusion: Our analysis provided a robust set of parameters to describe the population PK of ABC, which can be used to evaluate prospective study design, dosing regimens and covariate effects in children. The analysis also confirms the suitability of the model to inform the potential of a once daily dosing regimen in children of at least 3 months of age, as currently prescribed in adults.

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Verena Gotta I-24 Power of PKPD analysis to detect QTc effect in preclinical setting

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Objectives: This simulation study aimed at investigating the power of PKPD modeling to detect different magnitudes of QT-prolongation in preclinical cardiovascular safety studies in the conscious telemetered dog.

Methods: A PKPD model predicting individual corrected QT intervals (QTc, linear correction to a heart rate of 60 bpm) was developed for the positive control drug sotalol from a standard cardiovascular safety study: 6 animals received on 4 occasions in a crossover setup a vehicle, low, mid and high dose [1]. Maximal plasma concentration (C_{max}, population prediction) at the high dose level was 15 777 ng/ml. The model described QTc over 24h as a function of circadian variation (cosine function) and drug concentration (sigmoidal E_{max} model, E_{max}=50.8 ms, EC_{50}=1780 ng/ml), while drug concentrations were described by a simple 1-compartment model. The residual variability in QTc was 8.5 ms. This “true” model was simulated 100 times for each study investigating 3%, 1% and 0.5% of the original dose levels, with expected drug-induced QTc prolongation (ΔQTc) at high-dose population C_{max} of 11.5, 4.8 and 2.6 ms. Because simulated drug concentrations were very low compared to EC_{50}, the simulated studies were re-estimated using a linear model (model 1) and a model not including a drug effect as reference (model 2). A drop of the objective function by 3.84 (likelihood ratio test, alpha = 5%) was considered as significant.

Results: The power of detecting a drug effect was 100%, 98% and 74% at 3%, 1% and 0.5% of the original dose level, respectively. Mean estimated ΔQTcs [95% prediction interval] were 11.7 [8.8-14.7] ms, 4.8 [2.7-6.8] ms and 2.6 [0.8-4.2] ms, respectively.

Conclusions: Compared to the reported power of conventional statistical methods (80% for detecting a 4 ms [2] and 10 ms [3] QTc effect, respectively), these preliminary results suggest superior sensitivity of model-based approaches to quantify QT prolongation in preclinical setting. This underscores the value of PKPD modeling in preclinical safety testing.

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Michael Heathman I-28 Concentration-Response Modeling of Adverse Event Data using a Markov Chain Approach

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Objectives: The most common treatment-emergent adverse events for an experimental drug (LY) were gastrointestinal, with nausea (N) and vomiting (V) among the most frequently reported. The incidence of N/V was dose dependent and greatest after the first dose of LY, at approximately the time of maximum concentration (day 2 to 3). Incidence of N/V declined rapidly after the first 2 weeks of treatment. The development team was interested in whether patients would benefit from dose titration at the Phase 3 dose levels.

The objective of this analysis was to develop an exposure-response model to characterize the relationship between LY concentration and the onset, duration, and severity of N/V, as well as the development of tolerance. The model was used to simulate N/V under various dose titration regimens.

Methods: A Markov Chain model was developed, with N/V severity incorporated as different states within the chain. The onset and duration of events were governed by the transition probabilities among these states. As N/V incidence was observed to track the LY concentration profile, longitudinal predicted concentrations from a previously developed pharmacokinetic model were used for exposure-response. These concentrations were included as modifiers on the transition probabilities to affect onset, duration, and severity. Development of tolerance was incorporated using effect compartments.

The resulting model was used to simulate N/V incidence over the course of various dose titration regimens.

Results: Increased LY concentration was found to increase the probability of N, regardless of the previous state, and to increase the probability of remaining in a moderate/severe N state. Probability of V depended on the previous N state, and increased with increasing concentration. Sustained exposure to LY was found to cause tolerance, decreasing the probability of both N and V.

There was no significant reduction in the model-estimated incidence of N/V with titration regimens that initiated with a low LY dose for 1 or more doses, before titrating to a higher dose.

Conclusions: The Markov Chain approach characterized the LY concentration-response relationship for onset, duration, and severity of N/V events, as well as the development of tolerance. The model-based evaluation of N/V supported that dose titration would not improve the overall incidence of N/V during initial treatment.

Jay Mettetal II-24 Preclinical cardiovascular risk assessment of PPAR-gamma agonist effects based on translational PK/PD modelling

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Objectives: Safety margin assessments due to PPAR-gamma activity in toxicological studies is often confounded by study length and species sensitivity [1]. Here we attempt to increase the interpretability of these studies by comparing the TK/TD relationships of known PPAR-gamma agonists between dog, a key toxicological species, and man.

Methods: To assess the effects of PPAR-gamma agonist activity on the cardiovascular system we examined hematocrit and haemoglobin, markers of plasma volume expansion [2], under chronic dosing in dog and man for rosiglitazone and tesaglitazar, both potent PPAR-gamma agonists. Models describing the time-course of hematocrit and haemoglobin reduction were then established in both species.

Results: Indirect response models with linear dose-dependent inhibition on production were used to describe the time-course of plasma volume expansion, based on hematocrit and haemoglobin reduction, during both treatment and recovery. The parameter determining the timescale of haematological effect was broadly comparable across compounds and species reflecting slow changes to haematological endpoints. The sensitivity to drug was likewise assessed and differences compared between species and compounds.

Conclusions: The models developed provide a mechanism for interpretation of preclinical toxicological findings by increasing translatability of findings between studies of different duration as well as between species.

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Hyangki Choi III-37 Population PKPD modeling of moxifloxacin effect on QT interval prolongation from baseline in Korean and Japanese healthy male and female subjects

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Objectives: To develop population PKPD models describing the relationship between moxifloxacin and corrected QT interval prolongation in Korean and Japanese.

Methods: Population pharmacokinetic (PK) and pharmacodynamic (PD) modeling of moxifloxacin was developed from pooled data from Korean male (n=10), female (n=10) and Japanese male (n=10), female (n=9) volunteers. The PK modeling used plasma concentrations of the moxifloxacin and the PD modeling used QT interval prolongation adjusted for circadian variation. The models were developed using NONMEM and evaluated via visual predictive check (VPC).

Results: Data were fitted by 2-compartment model with first-order absorption elimination. There was no statistically significant covariate for each model parameter. The typical point estimates of PK were ke ,elimination rate constant = 0.03 h(-1), V2 ,volume of central compartment = 96.9L, and V3 ,volume of peripheral compartment = 302L. The typical point estimates of PD were Emax ,maximum difference of corrected QT interval from baseline = 30msec , EC50 ,median effective concentration = 5.81 ug/mL, and BASE value ,predose corrected QT interval = 397msec.

Conclusions: The final PK-PD model of moxifloxacin adequately described the observed QT interval prolongation in healthy Korean and Japanese subjects. The model developed in this study could be applied in guiding further clinical development of moxifloxacin in Korea and Japanese population.

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William Denney III-51 What is Normal? A Meta-Analysis of Phase 1 Placebo Data

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Objectives: To summarise all adverse events (AE), vital signs, electrocardiograms (ECG), and lab measurements for healthy subjects receiving placebo in First in Human (FIH) and Multiple Ascending Dose (MAD) studies in Pfizer's Phase 1 Management System (PIMS) to aid in the interpretation of 'What is Normal?' and to provide informative prior distributions for Bayesian analyses.

Methods: All AE, vital sign, ECG and lab measurement data for healthy subjects receiving placebo in FIH and MAD studies were selected from PIMS. AEs were classified using MedDRA 15.0, lab names and units were standardized and baseline was selected as nominal time equal to zero or any point a multiple of 24 hr prior in the same treatment period. AEs were summarised by numbers and percentages of events, subjects, and studies with events. Additionally the distribution of percentage occurrence by study was summarised for common AEs. For vital signs, ECGs, and lab measurements, baseline, raw values, and change from baseline were summarised using distribution quantiles, histograms, and empirical distribution functions. Any numerical measurements with at least 100 subjects were modelled with a linear mixed effect model testing demographic parameters as fixed effects and random effects on intercept by study and subject within study using the lme4 function in R [1]. Model fits for single and multiple covariates were obtained; the latter were estimated using an automated stepwise modelling procedure.

Results: The final data summarised were for 1204 subjects from 82 FIH and MAD studies. Updated ranges for extreme values of labs, vitals, and ECG measurements have been generated, and the importance of demographic parameters on measurements (or lack thereof) has been estimated with many subjects and dense measurements. The results were summarized and posted to an internal website allowing rapid queries without requiring specialized tools.

Conclusion: The analysis has allowed classification of potentially abnormal measurements incorporating the large data set of placebo subjects in similar populations—the placebo population within the current study can be augmented and anchored by historical data. It has also provided data that can be used for the formation of informative prior distributions for future Bayesian analyses. The analysis of healthy subjects has enabled a more thorough estimate of what is normal and quantification of potentially abnormal signals in early clinical development.

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Farkad Ezzet I-04 Dose Response Models for Multiple Endpoints: A Simulation Study

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Objectives: There are potential advantages in modeling multiple endpoints simultaneously in a single model fit: 1) perform tests on shared parameters between endpoints and 2) ability to establish models when one or more endpoints are less frequently observed. Using simulation we aim to explore the performance of a bivariate dose response model.

Methods:

Consider $Y_{ij,k}$ to be the response for k^{th} endpoint for the i^{th} subject when treated with the j^{th} dose,

$$Y_{ij,k} = f_k(\underline{g}_{ij}) + \{ d_{1k} + f_k(\underline{g}_{ij})^{d2k} \} e_{ij,k}, \quad k=1,2,\ldots,M$$

The parameters d_1 and d_2 alongside $e_{ij,k}$ (assumed $N(0, s_k^2)$) describe an additive and power error model, with $s_k = g_k s_1$, where, g_k is the fold difference in standard deviation of the for k^{th} endpoint. Data set is created by stacking observed responses as a single Y variable with a flag identifying the M endpoints. Consider 2 endpoints following an inhibitory and a stimulatory E_{max} models:

$$Y_{ij,1} = placebo_1 e^{h1i} [1 - I_{max} \{ Dose_{ij} / (Dose_{ij} + ID_{50}) \}]$$

$$Y_{ij,2} = placebo_2 e^{h2i} [E_{max} \{ Dose_{ij} / (Dose_{ij} + ED_{50}) \}]$$

A data set (N=24) from a 5-period X-over was simulated. Subjects received placebo and 4 doses of 0.1, 1, 10 and 100 mg. The two endpoints are observed once after each treatment. Parameter values were, $placebo_1$=50, $placebo_2$=5, I_{max}=0.8, E_{max} =1, ID_{50}=ED_{50}=1, h_1=h_2=0.01, s_1=s_2=0.05, d_1 =1.5, and d_2 =1. Simulated data for the two endpoints were fitted simultaneously and independently. A cross-endpoint hybrid metric such as ID_{80}/ED_{20} is of interest. Metric distribution was compared using the two methods based on simulated data repeated 1000 times using Splus.

Results: Modeling multiple responses was feasible under a general model and error structure. For the bivariate case discussed above, model estimates were in close agreement with the true values. Additional results will report comparisons with independent models under various data settings, including unequal endpoint sample size.

Conclusions: Modeling multiple endpoints in a single-model fit offers a means of estimating and comparing drug effects on multiple endpoints.

Ignacio Gonzalez I-20 Simulations of populations with different creatinine clearance range and weight to select the best dose of NV22413

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Objectives: The aim of our work was to analyse the best dose schedule in order to achieve similar drug exposure that the one achieved in the ongoing Phase III study (effective concentrations), simulating population groups with three different creatinine clearance and weight ranges.

Methods: NV22413 was previously fitted to a population PK model according to a two-compartment model with 3 transit compartments in the absorption process. Creatinine clearance and weight were statistically relevant covariates affecting to clearance and central volume, respectively. Population groups varying in creatinine clearance ranges (30-70, 70-100, >100 ml/min) were simulated and the exposure at five different doses was estimated: 1, 16, 30, 45, 60 mg once daily for each creatinine clearance level, In order to avoid situations where the relationship between creatinine clearance and body weight was unlikely, a correlation was established between weight and creatinine clearance. The simulated exposure levels were obtained by 1000 simulations of one patient for each clearance creatinine group using NONMEM 7.2 [1] and PsN 3.7.6 [2].

Results: The best dose schedule for population with the normal creatinine clearance (>100 ml/min) is 45 mg of NV2213 once per day, due to this dosing scheme achieves the highest percentage of the effective concentrations (87%). Nevertheless, for patients with lower clearance creatinine (

Conclusion: For patients with a normal value of clearance creatinine the best scheme of treatment is 45 mg once daily. In a previous study, the same dose was chosen to get the effective concentration in the population. However, when the creatinine clearance is diminished it is recommended to reduce the dose to 30 mg once daily.

References:

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[2] Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)-a Perl module for NONMEM related programming. Comput Methods Programs Biomed. 2004 Aug;75(2):85-94.

Kristin Karlsson I-46 Estimating a Cox proportional hazard model in NONMEM

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Objectives: Traditionally the most commonly used model for survival analysis is the Cox proportional hazard (Cox PH) model [1]. The Cox PH model is a semi-parametric model that makes a parametric assumption regarding the effect of the covariates on the hazard function, but makes no assumption about the shape of the hazard function (i.e. the baseline hazard). This can be interpreted as it is the influence of the covariates that are of interest, not the nature of the hazard function as such.

As time to event models are increasingly used within the field of pharmacometrics it would be convenient to be able to add the Cox PH model to the battery of survival models to be tested in NONMEM and to be used within other procedures such as scm or sse in PsN [2]. Hence, the objective of this work was to implement the Cox PH model in NONMEM® [3].

Methods: The log partial likelihood for the Cox PH model with the Breslow approximation [4] is defined as: $\log L=\sum_j^N\{S_i\beta- d_j*\log[\sum_{k\in Rj}\exp(X_k\beta)]\}$ where N is the last observation in the data set, R_j is the set of subjects at risk at time *j*, X_k is the covariate vector for subject *k*, β is the covariate coefficient vector, $S_i=\sum_{i\in Dj} X_i$, where D_j is the set of subjects having an event at time *j* and d_j is the number of events at time *j*. This definition of the likelihood, which allows for tied event times, was implemented in NONMEM®. As the risk set at time *j* (R_j) consists of the included subjects with event/censoring time ≥ j the data set was sorted according to decreasing event times, enabling the inner sums to be calculated on the fly. The implementation was tested on a data set which was simulated based on the survival model presented in Bruno et al [5]. Four covariates were tested: baseline tumor size, tumor size at week 6 (as time constant), number of metastases and ECOG status. The result from NONMEM® was compared to a Cox PH model run in R.

Results: The estimated covariate coefficients in NONMEM were: 0.00428, 0.792, 0.518, 0.189, and the same in R (with the Breslow option): 0.00429, 0.792, 0.519, and 0.189. The standard errors of the estimates were also equal between the software.

Conclusions: The likelihood for the Cox PH model with the Breslow approximation was successfully implemented in NONMEM® with the presumption that the subjects in the dataset are ordered by decreasing event times.

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Markus Krauß I-57 Hierarchical Bayesian-PBPK modeling for physiological characterization and extrapolation of patient populations from clinical data

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Objectives: The identification of interindividual variability from clinical pharmacokinetic data using a hierarchical Bayesian approach in combination with large-scale physiologically-based pharmacokinetic modeling; and the physiological characterization and refinement of populations with potentially critical pharmacokinetic response to drug exposure.

Methods: On the one hand, physiologically-based pharmacokinetic (PBPK) modeling characterizes a mechanistic approach for a highly detailed description of the key absorption, distribution, metabolization and excretion (ADME) processes in the body. Large amounts of prior data about anthropometric and physiological parameters are integrated into PBPK models to mechanistically evaluate the processes governing pharmacokinetics (PK) behavior. On the other hand, a hierarchical statistical model was used in combination with a Bayesian approach to systematically account for parameter variability and uncertainty at the population and the individual level. To cope with the high dimensionality of the approach, Markov chain Monte Carlo approaches were used.

Results: By the consideration of the PK of several drugs in small cohorts of healthy volunteers the advantages of the combined approach of Bayesian-PBPK are illustrated. The ADME processes showed large variability. Additionally, several physiological parameters were informed by the experimental data, which allows refining the physiological database concerning such parameters. The resulting posterior distributions of all integrated parameters were then used for extrapolations of a large population of healthy individuals to evaluate the effective range of the drug as well as critical dosings.

Conclusions: The presented Bayesian-PBPK population approach systematically characterizes and quantifies interindividual variability at the population level and the parameter uncertainty at the individual level. Due to the separation of physiology, ADME processes and drug physicochemistry the translational learning of physiological parameters is possible. This allows a thorough characterization and prediction of specific properties of special populations like pediatric or diseased populations.

Sean Oosterholt II-39 Covariate model selection in an Alzheimer disease progression model

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Objectives: Although in the past two decades hundreds of molecules were tested against Alzheimer disease (AD) only five for symptomatic treatment were approved, the last one in 2003. Regulatory agencies have recently recognized the importance of simulation modelling tools to better design clinical studies and consequently decrease the high drug development attrition rate for this indication [1]. Population characteristics are an important determinant in AD studies and therefore, an exhaustive assessment of the relationships between parameters and population covariates would be highly valuable. In this work we used the ADAS-cog indirect response model published by Gomeni et al [2] as base model, then the covariate models were selected using a multi-study dataset.

Methods: The analysis was done on placebo/background therapy data from 10 aggregated AD studies for the CAMD initiative [3]. Together the studies offered a wide range of patient characteristics, in terms of demographics (age: 73 ± 8.1, 55% female) and disease features (bMMSE: 20 ±3.8, ADAS-cog: 23.5 ± 9.9). Parameter-covariate relationships were assessed using stepwise covariate model building (SCM) alone or in combination with different validation methods; e.g. a bootstrap SCM. Tested covariates included age, baseline MMSE and gender, while the considered parameter-covariate relationship states were: linear, exponential and power. With the exception of the standard SCM, all methods used a linearization procedure and allowed the parallel evaluation of the parameter-covariate states. To verify the relevance of the selected covariates a bootstrap was performed on the final model. Modelling analyses were executed using NONMEM 7.2 and PsN 3.4.2. Data manipulation, as well as graphical and statistical summaries were done in R 3.0.2.

Results: Standard SCM method selects 7 or 8 out of the 12 possible relationships with and without linearization respectively. The bootstrap SCM narrows down the results to 3 relations selected more than 80% of the time. Gender did not result to be a relevant covariate. Age and baseline Mini Mental State Examination (bMMSE) were selected at least 85% with all parameters showing a dependency on bMMSE.

Conclusions: Using an automated tool for the covariate model building we were able to confirm the inclusion of a subset of covariates on the base structural model published in [2], even when applied to a wider dataset.

References:
[1] http://c-path.org/wp-content/uploads/2013/09/CAMD-AD-Model-press-release.pdf
[2] Gomeni R et al. Alzheimer's & Dementia 8 (2012) 39–50
[3] Coalition Against Major Diseases; http://www.c-path.org/CAMD.cfm

Francesco Bellanti III-13 New dosing recommendations in patients receiving deferiprone chelation therapy in the presence of renal complications

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Objectives: To characterise the pharmacokinetics of deferiprone [1, 2] using a model-based approach and assess the effect of demographic and physiological factors on drug exposure; and to evaluate the adequacy of the current dosing regimen in patients with renal impairment.

Methods: Data from 55 adult healthy subjects receiving deferiprone (solution 100 mg/ml) were used for model building purposes. A population pharmacokinetic analysis was performed using NONMEM VII. The contribution of gender, age, weight, and creatinine clearance on drug disposition was evaluated according to standard forward inclusion, backward deletion procedures. Model selection criteria were based on graphical and statistical summaries.

Results: A one-compartment model with first order oral absorption was found to best describe the pharmacokinetics of deferiprone. Goodness-of-fit plots, visual predictive check (VPC) and NPDE summaries indicated that the model provides an unbiased description of the data. Simulated AUC and Cmax were comparable with literature references [3, 4, 5]. Gender differences in the apparent volume of distribution (20% difference) have been identified, which may contribute to an increase in peak concentrations in females. Furthermore, simulation scenarios reveal that dose adjustment is required for patients with reduced creatinine clearance. Doses of 60, 40 and 25 mg/kg for patients showing mild, moderate and severe renal impairment are proposed based on creatinine clearance values of 60-89, 30-59 and 15-29 ml/min, respectively.

Conclusions: Our analysis has enabled the assessment of the impact of gender and creatinine clearance on the pharmacokinetics of deferiprone. Moreover, it provides the basis for dosing recommendations in renal impairment. The implication of these covariates on systemic exposure is currently not available in the prescribing information of deferiprone.

References:
[1] Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. Acta Haematol. 2009; 122(2-3):155–64.
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Julie Bertrand III-15 Population approach in high-throughput pharmacogenetics: challenging the maximum likelihood approaches and exploration of a Bayesian alternative

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Context: In a previous study, we have shown that an integrated approach, simultaneously estimating the PK model parameters and the genetic size effects, was, on a rich design, just as powerful as the classical stepwise procedure for covariate building to detect the effect of 6 causal variants from a large single nucleotide polymorphisms (SNPs) array [1].

Objectives: To challenge the integrated approach and the classical stepwise procedure on i/ genetic predictors of multiple PK parameters and ii/ a challenging study design. To explore a Bayesian alternative.

Methods: We simulated a two compartments PK model, with parameter values from a real-case study. From the initial scenario with N=300 subjects/n=6 sampling times and the effect of 6 SNPs on the apparent elimination clearance (CL/F) only, we now simulated i/ one scenario with the same design but the effect of 2 pairs of correlated SNPs each affecting CL/F and the central compartment apparent volume of distribution and ii/ one scenario with the same 6 causal variants on CL/F but 700 supplementary subjects having only a trough concentration.

Our integrated approach includes a penalized regression at each iteration of the Stochastic Approximation Expectation Maximization algorithm. Two penalization are considered here; Lasso and its generalization with heavier tails, HyperLasso. The full-Bayesian alternative is implemented in R using the R2jags package. For the SNP effect size we used a double-exponential (DE) prior to mimic Lasso shrinkage. The penalty parameters are set to ensure a 20% family wise error rate using an asymptotic approximation-based formula corrected for the information in the design.

Results: When genetic predictors affect multiple PK parameters, the integrated approach is more powerful than the stepwise procedure with 637 (Lasso) and 639 (HyperLasso) versus 596 true positive (on a maximum of 800).

References:
[1] Penalized regression implementation within the SAEM algorithm to advance high-throughput personalized drug therapy. Bertrand J, Bading DJ, De Iorio M. PAGE 2013.

Mano Chetty III-36 Exploring fixed dose versus body weight based dosing for monoclonal antibodies using physiologically based pharmacokinetic modelling.

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Objectives: To determine whether physiologically based pharmacokinetic (PBPK) models, which incorporate covariates and interindividual variability in systems parameters, are effective in predicting whether fixed dosing or weight based dosing is more appropriate for specific monoclonal antibodies (mAbs).

Methods: The Simcyp Population Based Simulator was used to simulate concentration-time profiles for omalizumab (150mg and 300mg) and efalizumab (1mg/kg and 10mg/kg) using the study designs of published clinical studies[1,2]. The suitability of the models was verified by comparison of the simulated pharmacokinetic (PK) profiles with those observed clinically. Using these models and 500 virtual healthy volunteers, PK profiles were simulated for each mAb using both dosing options and four single doses (ie. omalizumab 2mg/kg and 4mg/kg and efalizumab 75mg and 750mg, in addition to the above doses). The means of the area under the plasma concentration versus time curve (AUC_{0-t}) and maximum plasma concentration (Cmax) for each weight group were compared for variability with the two dosing options after stratifying population by weight (40 – 50 kg; 51-60 kg; 61-70kg; 71-80kg; 81-90 kg; 91-100 kg; 101-110kg; ≥111kg). Variability was evaluated by the fold difference (>2 fold was considered to be significant) between the lowest and highest value for each of the above PK parameters, using the mean of the predicted values for the different weight groups.

Results: Observed PK profiles for omalizumab and efalizumab were successfully recovered with the Simcyp minimal PBPK model for therapeutic proteins and the mechanistic FcRn model, respectively. Variability in Cmax and AUC of efalizumab was significantly higher when the fixed doses were used. No clear trends in variability between the weight groups using the two dosing approaches was observed for omalizumab. The fold differences in AUC (>2 fold) and Cmax (>2 fold) suggested that weight based dosing is more appropriate for efalizumab. Decisions on dosing for omalizumab may require further investigation since there is no clear advantage of one approach over the other. These predictions correspond with dosing recommendations for these mAbs, where weight based dosing had been used for efalizumab while omalizumab dosing is based on an algorithm with mg/kg and IgE level.

Conclusions: This preliminary study suggests that simulations using PBPK modelling can be useful in predicting suitability of dosing options for mAbs.

References:
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Chenhui Deng III-50 Within subject variability in pharmacometric count data modeling analysis: dynamic inter-occasion variability and stochastic differential equations

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Objectives: Parameter variation in studies can be characterized as within subject variability (WSV) in pharmacometric models. WSV has previously been successfully modeled using inter-occasion variability (IOV) [1], but also stochastic differential equations (SDEs) [2]. Studies with count data as endpoint are often long-term with frequent recordings and WSV can be expected to be important. However, the traditional IOV implementation method (IOV) necessitates occasions to be predefined and, to the best of our knowledge, SDEs have so far only been applied to continuous models. Hence, this study aims to develop and evaluate approaches addressing WSV in count models based on IOV and SDEs.

Methods: Base models were derived from a Poisson distribution, where λ accounts for mean count. A dynamic IOV (dIOV) approach was applied to depict the change of IOV over time on λ or other parameter; it used a sum of sequential functions involving the parameters: occasion length, amplitude and shape factor. The implementation of SDEs [2] was adapted to estimate parameter variability on λ. The models were fitted to 2 published pharmacodynamic data sets, seizure counts [3] and Likert pain scores [4]. In addition, IOV with occasion length fixed to the estimate of dIOV was conducted. Likelihood ratio test and graphical evaluation were used to quantify the potential improvement of model-fit in comparison to the published models. Simulations were used to explore further the capabilities of the two approaches.

Results: When WSV was defined as IOV, the OFV drops compared to a model without WSV were only 84 (df=2) and 227 (df=2), for the seizure count and Likert pain score data sets, respectively. The corresponding decreases for dIOV models were 201 (df=4) and 1022 (df=6), where in the latter data set IOV and dIOV were introduced on both λ and the inflated probability of change in score. When including SDE in the models, the OFV dropped by 159 (df=2) and 1421 (df=1), respectively. Simulations confirmed the systematic gains in introducing WSV as dIOV or SDE compared to IOV and enabled model misspecification detection when present.

Conclusions: The proposed approaches in this study offer strategies to characterize WSV in count data models. The developed dIOV method can capture the change of IOV over time in rich long-term studies and improve model-fit. The adapted SDE approach can be applied to quantify parameter variability and detect model misspecification.

References:
[1] M.O. Karlsson *and* L.B. Sheiner, JPKB, 21 (6), 1993 [2] C.W. Tornøe, *et al.,* Pharmaceutical Research, 22 (8), 2005 [3] I.F. Trocóniz, *et al.,* J PK&PD, 36, 2009 [4] E.L. Plan, *et al.,* CPT, 91(5), 2012

Serge Guzy I-26 Evaluation of Bias and Precision using QRPEM algorithm in Phoenix NLME for discrete data models

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Objectives: The aim was to investigate and compare the performance with respect to bias and precision of the QRPEM and LAPLACE methods available in Phoenix NLME for discrete data and repeated time to event data.

Methods: Discrete data models with “mu-modeled” parameters, representing different types, binary, count, ordered categorical (OC) and a repeated time-to-event (RTTE) model were used to simulate 200 datasets that were subsequently re-estimated using Phoenix NLME (v1.4 beta). Each model was simulated with different starting values for the random effects representing low, medium and high between subject variability on the fixed effect parameter estimates, resulting in ten different scenarios. All datasets in each scenarios were analyzed starting with initial estimates set to the true simulation values of that scenario. Root mean squared error (RMSE), relative bias (RB) and relative estimation error (REE) in estimates were evaluated for each parameter across scenarios.

Results:QRPEM performed equal or better as compared to LAPLACE across all scenarios investigated. The absolute RB was less than 5 % for fixed effects and in the range of 10-20 % for random effects parameters. The RMSE was less than 5 % across all different models and scenarios. On an average the runtimes for LAPLACE were quicker than QRPEM.

Conclusions: We present preliminary results evaluating the new QRPEM algorithm in Phoenix NLME for discrete data models. As all parameters were “mu-modeled”, this evaluation tested QRPEM specifically as opposed to using Sampling Importance Resampling algorithm (SIR). QRPEM performs equal or better than LAPLACE in most scenarios, with the bias on random effects higher than fixed effects. Further evaluation of QRPEM and comparison to similar algorithms in other software is currently in progress which will allow a complete evaluation with respect to discrete data models.

Nick Holford I-34 Evaluation of NONMEM and Monolix by Parametric Bootstrap

Nick Holford
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Objectives: To evaluate NONMEM and Monolix in terms of parameter estimation bias and uncertainty coverage bias using a parametric bootstrap procedure.

Methods: Default SAEM estimation options (NONMEM AUTO, Monolix algorithms options created when no algorithms file supplied as input) were used. All calculations were performed using the NeSI PAN cluster. Four problems of increasing difficulty were tested: warfarin pharmacokinetics, simple and complex tumour growth inhibition, viral load kinetics. Uncertainty bias was based on the bootstrap standard deviation relative to the standard error which described 95% coverage of the bootstrap distribution.

Results and Conclusions: NONMEM was less biased in terms of parameter estimates (see Table 1 for tumour growth inhibition [1] example). Both methods had biased uncertainty relative to bootstrap coverage (Table 2). Some problems were better described using FOCE while others were better described using SAEM.

Table 1 Estimation Bias for Model Parameters

Tham TGI		NONMEM	NONMEM	Monolix
Method		FOCE	SAEM	SAEM
Option		INTER	AUTO	No algo
Parameter	TRUE	MDL	MDL	MDL
POP_SIZE0	6.39	-2%	1%	2%
POP_TOVER	33.9	10%	33%	1980%
POP_AE50	6324	8%	-23%	138%
POP_TEQ	4.407	37%	-6%	393%
PPV_SIZE0	0.6	-3%	-3%	-7%
PPV_TOVER	0.420	-46%	30%	366%
PPV_AE50	1.200	-15%	-15%	-44%
PPV_TEQ	0.200	-39%	109%	394%
RUV_CV	0.199	-0.3%	-1%	2%

TRUE=Parameter used for simulation MDL=Model parameter bias

Table 2 Uncertainty Bias for Model Parameters

Tham TGI	NONMEM	NONMEM	NONMEM	Monolix
Method	FOCE	FOCE	SAEM	SAEM
Option	INTER		AUTO	No algo
Parameter	95 SE	AsymRSE	AsymRSE	AsymRSE

POP_SIZE0	9%	-5%	15%	-3%
POP_TOVER	57%	-4%	82%	161%
POP_AE50	72%	33%	40%	-48%
POP_TEQ	85%	-13%	-9%	-19%
PPV_SIZE0	8%	13%	48%	31%
PPV_TOVER	143%	47%	246%	-46%
PPV_AE50	45%	-29%	201%	6%
PPV_TEQ	178%	193%	53%	-52%
RUV_CV	6%	1.6%	63%	7%

95SE= standard error which described 95% coverage of the bootstrap distribution

AsymRSE=bias of asymptotic relative standard error relative to 95SE

References:

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Jacob Leander II-08 Estimation in stochastic differential mixed-effects models

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Objectives: The model dynamics is often assumed to be deterministic in traditional mixed-effects modeling. We want to extend the non-linear mixed-effects model to a so called stochastic differential mixed-effects model, to account for model deficiencies and uncertainty in the dynamics [1-4]. In extension to previous results, interactions between the output covariance and the random effects, together with correlation between random effects are considered. Moreover, we aim for a robust calculation of the gradient of the objective function by using sensitivity equations.

Methods: The ordinary non-linear mixed-effects modeling framework is extended by considering stochastic differential equations. The population likelihood is approximated using Laplace's approximation together with the First Order Conditional Estimation with Interaction (FOCEI) method. The state variables of system (e.g., drug concentration) is estimated using the extended Kalman filter on an individual level. In contrast to the commonly used finite difference approximation of the gradient we utilize the so called sensitivity equations. These equations provide a robust and efficient evaluation of the objective function and its gradient. They are obtained by differentiating the update and prediction equations in the extended Kalman filter.

Results: An algorithm for parameter estimation in stochastic differential mixed-effects models has been developed. It features sensitivity equations for a robust and efficient calculation of the gradient in both the outer and inner optimization problem. The stochastic differential mixed-effects framework is illustrated by using a pharmacokinetic model of nicotinic acid (NiAc) turnover in obese rats [5-7]. The analysis shows that the total error consists of pure measurement error together with a significant uncertainty in model dynamics. The smoothed state variables estimates are used to provide a visualization of uncertainty in variables after the parameter estimation has been completed.

Conclusions: We account for three sources of variability by considering stochastic differential mixed-effects models. We are able to account for uncertainty in the dynamics, in addition to measurement noise and interindividual variability. The new model structure is able to handle interaction effects and correlation between random parameters. The uncertainty plots derived from smoothing serve as an illustrative way to understand output variability.

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Robert Leary II-09 Robust Importance Sampling for EM-based NLME Algorithms

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Context: For EM-based NLME algorithms such as QRPEM in Phoenix NLME and IMP in NONMEM, a Monte Carlo or quasi-Monte Carlo integration to estimate moments of a target posterior is performed using (usually) a Gaussian importance sampling distribution (ISD). The ISD is tuned to mimic the target distribution fairly closely in the modal region, while maintaining somewhat wider tails. Adequately satisfying both objectives can be difficult, but is critically important to the success of the overall NLME algorithm. The ISD mean and covariance are typically based on the estimated mean and covariance of the posterior from the previous iteration, but with a scale factor>1 applied to the covariance to widen the tails. The window of workable scale factors may be narrow, not knowable in advance, and the usual default value can easily fail.

Methods: The work of Hesterberg [1] suggests that the use of an ISD that is a 'defensive mixture' of two or more Gaussian distributions with differing tail coverage characteristics can be much more robust than a single Gaussian. Owen and Zhou [2] suggest use of Hesterberg's defensive mixtures in conjunction with control variates to improve accuracy and avoid possible pathologies in the mixture sampling case. We introduced both techniques into the QRPEM algorithm and compared the results with the traditional single Gaussian ISD on variety of models.

Results: Greatly improved robustness with respect to user mis-specification of the covariance scaling parameter was demonstrated with a defensive mixture of two Gaussian components relative to a single Gaussian. The width of the window of workable scaling factors increased dramatically, typically by more than an order of magnitude, thereby greatly reducing the possibility of NLME failure due to a poorly scaled Gaussian ISD. With respect to control variates, we could not detect any examples of the types of pathologies suggested in [2], but did find that the use of control variates noticeably improved overall accuracy and precision for a given sample size.

Conclusions: Defensive mixture importance sampling greatly improves the robustness of importance sampling-based EM algorithms for PK/PD NLME estimation.

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Anna Largajolli II-05 The OFVPPC: A simulation objective function based diagnostic

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Objectives: Ability to assess the model adequacy through appropriate diagnostics is crucial in pharmacometrics. Here we suggest a simulation-based model diagnostic, the OFVPPC, which relies on the information content present in the objective function (OFV) to detect model misspecifications, outliers and estimation method limits.

Methods: From final model estimates 1000 stochastic simulations and estimations (SSE) implemented in PsN (1) were performed in NONMEM (2). The population (obsPOFV) and individual OFVs (obsIOFV) based on observed data were compared to the corresponding distributions of OFVs based on simulated data (simPOFV and simIOFV). In the SSE, a full estimation or an evaluation (MAXEVAL=0) of the model was performed. Both real data sets and simulations were used to explore these diagnostics.

Results: Model misspecification, both in the structural and stochastic model components, were often, but not always, clearly identified with POFVPPC. Indication of misspecification was evident from the obsPOFV being higher than the distribution given by the simPOFV. When the first-order method was used to estimate parameters, the short-coming of the method, increasingly for highly nonlinear models, was typically evident as a lower obsPOFV compared to the simPOFV distribution. Individual subjects with outlying data could often be identified from their obsIOFV being different from the corresponding distribution of simIOFV. In general, the same conclusion of misspecification regarding POFV and IOFV could be made regardless of whether full estimation was made of simulated data, or if only an evaluation (MAXEVAL=0) was performed. For IOFV, however, the use of MCETA, a new NONMEM feature that allows trying different set of initial estimates for the individual MAP estimation, could sometimes provide more reliable results when only evaluation was performed.

Conclusions: The OFV information, a sensitive measure that sums up the model fit, was exploited to build a diagnostic tool to be used during model building and for detection of outliers. The results of the OFVPPC are easy to visualize but similar to other simulation based diagnostic relies on the final critical judgement of the user.

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Rikard Nordgren II-36 Automatic binning for visual predictive checks

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Objectives: Visual predictive checks [1] require binning of the observations in the dimension of the independent variable. An automatic binning algorithm has previously been proposed [2]. In this study we explore a novel algorithm based on K-means clustering with a data density function to penalize adding a bin edge where the data is dense, and implement the algorithm in PsN [3].

Methods: For a given number of bins (K) the algorithm seeks to find the bin edges that minimizes the objective function O(K) = sum(W) + alpha*sum(Phi(e_i)), where sum(W) is the sum of within-bin variabilities, sum(Phi(e_i)) is the sum of the data density function values at the bin edges e_i, and alpha is a scaling factor. The data density function Phi is obtained by kernel density estimation using a Gaussian kernel [4]. The bandwidth for the kernel is chosen based on the optimal bandwidth for Gaussian data [4] but reduced by a factor F if the bin data appears non-Gaussian, as indicated by the kurtosis, increasing the resolution of Phi and decreasing the penalty for moving an edge into this area. Phi is computed based on an initial binning, were O_0 = sum(W) is minimized. The same optimization algorithm is used both for minimizing sum(W) to get an initial binning and for minimizing O(K) after Phi is fixed. The algorithm iterates between moving bin edges one by one within its two neighbors and taking out edges and placing them elsewhere. When the objective function cannot be reduced any further it stops. Finally the optimal K has to be selected. K that minimized O(K), the K that maximized the function used in a method proposed by Calinski and Harabaszs [5], and the ratio between the two were tried. The algorithm was run on test data and the resulting vpc plots were judged by a panel of experienced modelers to obtain reasonable values on the different parameters.

Results: The best values of the different parameters of the algorithm were judges to be alpha = 7.8*argmax_k(W), cutoff C=2.5 to classify the kurtosis as Gaussian/non-Gaussian, factor F=0.25 as the bandwidth reduction factor for non-Gaussian bin data, and the ratio between the objective function and the Calinski and Harabaszs function as the best K selection criteria.

Conclusions: We have developed an automatic binning algorithm that allows the modeler to quickly obtain a binning for VPCs. The user can either let the algorithm perform both bin edge placement and K selection, or let it place the bin edges given a user-selected K.

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Joakim Nyberg II-37 Simulating large time-to-event trials in NONMEM

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Objectives: Simulation of clinical trials is useful in e.g. model based power calculations, visual diagnostics during model building, predicting clinical trials and decision making. Simulating large time-to-event (TTE) trials is in NONMEM (NM) [1] traditionally performed using a dense grid dataset and utilizing the cumulative hazard to predict if an event occurred between two grid points [2, 3]. However, this method becomes impractical if the number of subjects is high, study is long and/or frequent grid points are needed, resulting in that a simulation data set may exceed 1 GB.

The objective of this work was to develop methods to perform TTE trial simulations in NM with precision in the simulations similar to dense grid simulations, but without huge input data sets.

Methods: With the developed method, using the original data set, the NM code simulates event times and based on these a table output with the resulting dependent variable at the event time is generated similar to the output obtained with dense grid data set simulation. The method was implemented for 4 parametric TTE distributions/survival functions: Exponential (E), Weibull (W), Gompertz (G), Log-Normal (LN), with covariate effects included proportional to the baseline hazard.

Two scenarios were investigated; S1) time independent covariates and S2) time dependent covariates, for a large data set (3 year study with ~14000 patients).

In S1, the event time was obtained using analytic solutions of the survival functions [4]. In S2, the survival function could not be solved analytically and event times was obtained using $DES with T and MTIME to assure that the implicit event grid was good enough for the acquired precision in the simulations.

Results: With S1, the study was simulated 100 times within 10 minutes with a total event data set size of ~65MB with a maximal precision (analytic). With time dependent covariates (S2) using at least a 1 day event precision (MTIME=0.5 days) 100 trials were simulated in less than 1 hour with a total event data set size of ~65MB compared to the grid solution of 1 day precision which had an input data set > 3 GB and could not be run with NM.

Conclusions: Efficient TTE trial simulations were implemented in NM without losing precision in the event time simulations. The technique is general and could easily be adapted to repeated TTE and to other models than those investigated. The precision for the S2 scenario could be further increased by decreasing the MTIME.

Acknowledgement: This work was part of the DDMoRe project.

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Acharya Chayan III-34 A diagnostic tool for population models using non-compartmental analysis: The nca functionality for R

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Objectives: Non-compartmental analysis (NCA) calculates pharmacokinetic (PK) measures related to the systemic exposure to a drug following administration, *e.g.* area under the concentration-time curve and peak concentration. We developed a new functionality in R, *nca*, to (i) perform diagnostic checks for a population model (PopPK diagnosis) and (ii) perform a traditional NCA.

Methods: The *nca* functionality estimates the PK measures by traditional NCA procedures [1] for the observed data set. For the PopPK diagnosis, a set of concentration-time profiles is simulated using the associated population model. The *nca* functionality estimates the PK measures for each simulated data set and compares them with those estimated from the observed data. The analysis is performed at the population as well as the individual level. The 95% nonparametric prediction interval of the distribution of the simulated population means of each PK measure is compared with the corresponding observed population mean. The individual level comparison is performed based on the deviation of the mean of any simulated PK measure for an individual from the corresponding observed value. The *nca* functionality also reports the normalized prediction distribution error (NPDE) of the simulated PK measures for each individual [2].

Results: The *nca* functionality produces two default outputs depending on the type of analysis performed, *i.e.*, PopPK diagnosis and regular NCA. The PopPK diagnosis feature of *nca* functionality produces 7 sets of graphical outputs to assess the ability of a population model to simulate the concentration-time profile of a drug and thereby identify model misspecification. In addition, tabular outputs are generated showing the values of the PK measures estimated from the observed and the simulated data, along with the deviation, NPDE, regression parameters used to estimate the elimination rate constant and the related population statistics. The tabular output for a regular NCA is similar to the output obtained in commercial software.

Conclusions: The *nca* functionality is a versatile and flexible tool-set written in R that successfully estimates PK properties from observed and simulated concentration-time data. It produces a comprehensive set of graphical and tabular output to summarize the statistical results including the model specific outliers. The output is easy to interpret and to use in evaluation of a population model.

Acknowledgement: This work was supported by the DDMoRe (www.ddmore.eu) project.

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Laurent Claret III-41 A simulation study to assess the impact of time to growth estimation shrinkage on overall survival association

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Objectives: Model based estimate of time to growth (TTG) of tumor sum of longest diameters (SLD) has been developed to predict overall survival (OS) in metastatic cancer patients in several diseases (1, 2). TTG is superior to earlier metrics such as tumor size ratio at landmarked time point (e.g. end of cycle 2). Recent correspondences and discussions have raised questions about this modeling approach (3-6). The tumor growth inhibition (TGI) observations are limited by the disease progression defined by an SLD increase of 20% for the minimum and/or death (RECIST). The objective of this simulation work is to evaluate the model parameter shrinkage on TTG estimate and the subsequent association with OS with limited number of observations.

Methods: TTG and OS of 500 patients were simulated based on previously published models (1). Several assumptions on the strength of the association (none to full) and on the time difference between TTG and OS were simulated to evaluate the impact on TTG and the TTG-OS association. TTG and the TTG-OS association were estimated by a two stage approach: 1) simplified TGI nonlinear mixed effect model (NONMEM, FOCE) to estimate TTG; 2) a cox proportional hazard semi-parametric model (coxph in R) to estimate the TTG-OS association. For each of 1000 replications the bias and the shrinkage of TTG and the TTG-OS association were evaluated. Alternative tumor size observation schedules were also evaluated in order to improve TTG estimate.

Results: The TTG shrinkage was about 40% (24%-60%) in the original scenario assuming median TTG of 24 weeks and median OS of 83 weeks. It could be reduced down to 35% if the patient follow up is up to 100% increase of the minimum recorded size instead of 20%. On the other hand shrinkage increased up to 50% when the OS survival time was divided by 2. In all scenarios assuming no TTG-OS association, the type I ($p<1\%$) errors were below 3% with a maximum risk when the median survival (83 weeks) was divided by 2 (41.5 weeks). The type II errors ($p<1\%$) were below 3% in scenarios assuming association.

Conclusions: Despite a relatively large shrinkage of TTG due to a limited number of observations the TTG-OS association does not seem to be impacted. This shrinkage depends on the time difference between TTG and OS and the observation schedule. TGI models are developed from the SLD as defined by RECIST (7), it would be worth to optimize tumor size observation schedule to extract more information on the TGI dynamic.

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Simon Zhou IV-56 Uncertainty and key factors in assessing drug effect in cell-based and xenograft tumor models in rodents

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Objectives: There have been poor concordance of IC50s by same drugs on identical cancer cell lines by different labs[1]. The goal of this investigation is to develop a mathematical model to capture the key driving forces of tumor growth/shrinkage and essential drug properties in order to better understand their impacts on the estimation of drug effect, eg. IC50.

Methods: A general mathematical model was developed and it well-characterized the drug exposure and tumor growth inhibition in both cell-based models and xenografted tumor models in mice. Closed form mathematical solutions were obtained for drug effect characterization in cell-based models and subjected to parameter sensitive analysis using derivatives. For the xenograft tumor models, numerical sensitivity analysis was conducted by simulations and subsequent PK/PD analyses to better understand the key drivers for tumor growth and shrinkage.

Results: The modeling and analyses indicated that innate tumor growth and death rate are the key driving force for tumor growth and shrinkage. In typical cell-based and xenografted models, the experimental observations are limited to cell number or tumor volume increase without any explicit measure of tumor death. IC50 cannot be accurately identified if high drug concentrations or high doses do not bring the cell number or tumor volume below the initial cell numbers or tumor volumes before drug treatment. And experiments producing qualitatively similar and clustered effects of tumor growth inhibition are not conducive for delineation of drug effect. Given usual experimental variability, different combinations of IC_{50}, K_g, and K_d could produce similar tumor inhibition profiles, further confounding the interpretation of the "true" drug effect.

conclusion: Large variation in drug effect estimation is inherent in either *in vitro* and *in vivo* models of tumor growth. Estimation of drug IC50 on tumor growth inhibition is highly sensitive to tumor growth rate and death rate. Reporting the baseline tumor growth rate with IC50 estimated will provide a less-biased measure for comparing different anti-cancer agents in vitro and in vivo.

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Sathej Gopalakrishnan I-23 Assessing treatment failure under combination therapy in HIV disease

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Objectives: The emergence of drug-resistant mutants remains a challenge to successful anti-human immunodeficiency virus (HIV) therapy [1]. Upon treatment failure, the choice of an optimal salvage therapy depends on the dominant viral mutant genotypes present. Our objective were (i) to assess genotypic reasons for therapy failure with multi-drug regimens and to determine how each drug in a combination-regimen individually affects treatment outcome; (ii) to demonstrate the benefit of regularization techniques developed for linear systems, in stabilizing parameter estimation for our nonlinear viral dynamics model.

Methods: We used a validated two-stage viral infection model [2] to predict *in vivo* HIV dynamics. We incorporated drug-specific mutation pathways and resistance factors estimated from clinical data (HIV Stanford drug resistance database [3]). See [4] for details. The fitness costs of different mutant genotypes that arose under anti-retroviral monotherapy with two different drugs – zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI) and indinavir (IDV), a protease inhibitor (PI), were estimated by simulated annealing [4]. To study the impact of regularization on parameter estimation, we used ridge regression [5]. Simulations and estimation procedures were carried out with MATLAB R2010b.

Results: We examined the fitness of the viral population during the course of treatment with ZDV and IDV and identified evolutionary bottlenecks in the path to full resistance. Simulations of the two-drug regimen showed that the viral composition at therapy failure strongly depended on drug efficacies. We identified combinations of individual drug efficacies where virological failure could be due to a) wild-type; b) PI-resistant mutations; c) NRTI-resistant mutations; or d) both NRTI and PI resistant mutations. Importantly, the times to failure with monotherapy regimens were not additive when predicting the time to failure with combination therapy. Finally, we showed that regularization techniques are beneficial in stabilizing estimates of fitness costs in our nonlinear model.

Conclusions: We demonstrated how clinical data from monotherapy can be leveraged to predict viral dynamics under combination regimens. This is a step towards studying potential salvage regimens upon treatment failure.

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Christoph Hethey I-30 Towards a cell-level model to predict bacterial growth under antimicrobial perturbation

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Objectives: Effects of antibiotics on bacterial growth are typically modeled by a direct change of growth or death rate of a bacterial population. Such an approach rarely allows to account for the mechanism of action in a mechanistic way - which is expected to be particularly relevant for the analysis of synergistic or antagonistic effects of antibiotic drug cocktails. The objective was to exploit known relationships between the population growth rate and the physiological state of a (typical) bacterial cell [1,2] to develop a cell-level population growth model, that allows to account for the effect of an antibiotic drug on the cellular level, causing a change in population growth rate.

Methods: The state of a bacterial cell was characterized by physiological descriptors, including measures for cellular functions like peptide elongation rate, fraction of active ribosomes and RNA polymerase activity. A functional relationship between these variables and the growth rate was estimated from data in [3]. For tetracycline, the pharmacodynamic effect on cell level was included as a change in the peptide elongation rate. Time kill curve data for E. coli were extracted from literature. Parameter estimation and simulations were performed in MATLAB (R2012a).

Results: Based on the functional relationships from cell state to growth rate and vice versa, we showed for a broad range of growth rates (0.3 - 3.0 doublings / h), that the predicted state of a (typical) bacterial cell allows to correctly predict its corresponding growth rate. For E. coli under exposure to constant concentrations of tetracycline, the model predicted time kill curve data in agreement with literature, based on the estimated reference state of a cell from control data.

Conclusions: For E. coli and tetracycline, we successfully showed that a cell-level bacterial growth model can be used to predict the impact of antibiotic perturbation on the population growth rate, i.e., growth and its change under antibiotic exposure is predictable from a cellular state of the bacterial cell. Extensions to include more drug classes are currently under development.

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Jules Heuberger I-31 The prior subroutine explored: pharmacokinetic modeling of THC

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Objectives: To evaluate the Prior subroutine in NONMEM® by comparing model results after using a Prior versus the standard method of pooling datasets. Both methods were used to develop a multi-compartment pharmacokinetic (PK) model for THC using clinical data, incorporating three major administration routes (oral, pulmonary, IV) and the long term PK of the cannabinoid tetrahydrocannabinol (THC).

Methods: For the PK modeling NONMEM® 7.2[1] was used. THC PK data were obtained from two inhalation[2,3], one oral[4] and a cross-over inhalation and IV administration studies[5]. The pooled data contains 910 THC plasma concentrations from 84 healthy volunteers. Using the traditional method, four datasets were pooled and modelled simultaneously. Secondly, three of the datasets were pooled and modeled. Results of this latter model were subsequently applied in the Prior subroutine to fit the fourth dataset, one of the inhalation studies. The results were then compared to the results of the traditional method.

Results: Both developed models accurately describe and predict THC plasma concentrations up to 48 hours after oral, pulmonary or intravenous dosing. Results for the standard model approach (with results of the Prior approach) show that THC has a fast initial and intermediate half-life, a relatively long apparent terminal half-life of 21 h (18 h), with a clearance of 38.9 L/h (38.1 L/h), systemic bioavailability 28.4 (26.3) % or 22.4 (25.6) % after inhalation with and without nose clip respectively. Remaining parameter estimates were also nearly identical, with a central volume of distribution of 6.17 (5.70) L, and rate constants to and from peripheral compartments of 1.3 (1.15), 0.04 (0.045), 4.10 (4.26) and 1.04 (1.16) /h. The Ka (1.99 /h), lag time (0.198 h) and oral bioavailability were identical, as the data fitted with the prior subroutine contained no oral input. Moreover, runtimes were reduced 17 times using the Prior subroutine.

Conclusions: Both model approaches describe the PK of THC accurately, with consistent parameter estimates. They can be applied to predict concentration-time profiles of THC after different dosing regimens (e.g. accumulation) for the mostly used administration routes. Also, the models can improve decision making in future clinical trials of (novel) cannabinoids. Model comparison showed that the Prior function in NONMEM® can be applied to fit prior results with new additional data rather than fitting a new model to an increased dataset, which will hence speed up model development.

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Gilbert Koch I-56 Solving Semi-Delay Differential Equations in NONMEM

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Objectives: Delay differential equations (DDEs) are a growing tool to describe delays and lifespans in pharmacokinetic and pharmacodynamic (PKPD) modeling [1]. Such equations are e.g. used to describe maturation of blood cells, incubation times in epidemics or strongly delayed phenomena like bone destruction in arthritis. In contrast to its ordinary differential equation (ODE) counterpart, a DDE describes a delay or lifespan with an explicit delay parameter T, is able to produce complex oscillating behavior and also includes information from the past, more precisely, the time before the PKPD system gets started. Currently, DDEs in its general form with a single delay

$x'(t) = f(t,x(t),x(t-T))\ ,\quad x(t)=x0(t)$ for $t\le 0$ (1)

could not be directly solved in NONMEM. However, we identified an important sub-class of DDEs (1), calling them Semi-DDEs, which are often used in PKPD modeling [1] and can be easily implemented in NONMEM. The general structure of Semi-DDEs with a single delay reads

$u'(t) = g(t,u(t))\ ,\quad u(t)=u0(t)$ for $t\le 0$ (2)
$v'(t) = h(t,u(t),u(t-T),v(t))\ ,\quad v(0)=v0$ (3)

where (2) is an ODE but equipped with a past u0(t) for $t\le 0$ and (3) uses the delayed state u(t-T) given by (2). Roughly speaking, Semi-DDEs (2)-(3) do not permit the rate of change of a state to be described by a right hand side which depends on its own delayed state.

Results: We will demonstrate that Semi-DDEs (2)-(3) could be simply rewritten by two systems of ODEs, one system for the time before delay T and one for the time after the delay. Applying the ALAG command and a case-by-case analysis, Semi-DDEs could be solved with NONMEM. As example we consider a Semi-DDE based PKPD model for rheumatoid arthritis [2] where inflammation and strongly delayed ankylosis was modeled.

Conclusions: We identified an important sub-class of DDEs, the so-called Semi-DDEs, which could be solved with standard ODE solver and therefore be implemented in NONMEM.

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Tafireyi Nemaura II-33 In silico estimation of oral bioavailability: Implications to estimation of efavirenz PK parameters.

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Objectives: To develop methods/models that enable better predictions of pharmacokinetic parameter estimates. There is possible new way of modeling which enables development of parameter estimates and allows for better prediction of what is occurring within the body. Instead of using the time variable space, in addition, it is possible to capture the effects that are attributable to the covariates as well by use of the developed covariate space.

Methods: Gender, middose plasma concentration, weight and CYP2B6, 516G>T genetic data of 61 patients on efavirenz containing HAART and on anti TB drugs was collated and analysed. Models were derived to estimate PK parameters that include bioavailability, elimination rate constant, volume of distribution and AUC using NONMEM, Partial Least Squares Regression, Regression methods.

Results: A new measure related to the uptake of the drug is incorporated in modeling of transportation (cumulative uptake volume). The cumulative uptake-volume associated with the full absorption of 600mg of Efavirenz was estimated to be 35.56L. An acceptable relationship was established between estimated oral bioavailability (f) and middose concentration (x) at steady state {$f = 0.2194+0.24388\ln x$, $R^2=0.97$, $p<0.00001$}. There was no patient below 1µg/ml in this population sample at middose concentration. Patients who carry the CYP2B6 G516T TT genotype are projected to have high efavirenz exposure. The estimated bioavailability in this population ranges from (0.29; 0.86).

Conclusions: Construction of a highly correlated variable to plasma concentration by Partial Least Squares regression enabled the development of a covariate measure. That enabled the estimation of oral bioavailability which then improves predictions of efavirenz plasma concentrations. Efavirenz is a drug that is well distributed in the fluid volume system. These relations are achieved from modeling with the aid of the covariate space.

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Elodie Plan II-50 Item Response Theory Model as Support for Decision-Making: Simulation Example for Inclusion Criteria in Alzheimer's Trial

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Objectives: Item Response Theory (IRT) has been introduced in pharmacometrics for the characterization of the Alzheimer's Disease (AD) Assessment Scale - cognitive subscale (ADAS-cog) test [1] and used as well in models describing the Expanded Disability Status Score in multiple sclerosis patients [2] and the Positive And Negative Syndrome Scale in schizophrenic subjects [3]. Benefits in terms of increased power of drug effect detection, enhanced simulation properties and quantification of item information content were highlighted. This study aims to demonstrate a practical application of IRT's distinct capabilities in the context of drug development (DD) decision-making. The fictitious example was an investigation of the DD question: which Mini-Mental-State Examination (MMSE) [4] inclusion range would deliver the highest probability to detect a hypothetical drug effect in a change from baseline (CFB) analysis of ADAS-cog as primary clinical endpoint for a coming AD trial?

Methods: The process followed an automated stochastic simulation and estimation approach repeated 500 times for different patient populations. The model used for simulation consisted of i) a previously published ADAS-cog IRT model [1], ii) an extension [5] linking the MMSE items to a common cognitive disability hidden variable, based on baseline records from the ADNI [6] database, and iii) a disease modifying drug effect of 30%. The simulations generated replicates of an 18-month placebo controlled trial with 600 subjects selected according to their sampled MMSE values. The estimations accounted for the mean CFB at the last visit using a repeated measures marginal means model. Constant progression rate, baseline correlation, and drug effect over cognitive disability were assumed in this study.

Results: The inherent properties of the simulation model captured several characteristics of the trial data, e.g., increasing skewness for lower MMSE ranges and ceiling/flooring effects of the ADAS-cog score. The power to detect the hypothetical drug effect for Alzheimer's patients having an MMSE score between 5-10, 10-15, 15-20, and 20-25, was 58%, 92%, 91%, and 74%, respectively.

Conclusions: The IRT pharmacometric approach allowed simulation of realistic clinical data and aided in answering the DD question even though a statistical analysis was intended for the fictitious trial. This example highlights the utility of complex IRT models for DD beyond the analysis of data.

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Nelleke Snelder IV-12 A new model-based approach to compare toxicity of a series of compounds based on their categorical toxicity scores

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Objectives: The toxicity of a series of new antibody-drug conjugates (ADCs) have been assessed pre-clinically. The outcome of these toxicity studies were summarized per tissue in different categories. The objectives of this analysis were to (i) determine an objective no-observed-adverse-effect-level (NOAEL) by establishing an exposure-response relationship for toxicity using this categorical data, (ii) rank the different ADC's according to their toxicity for pre-clinical screening.

Methods: Single end-point studies were conducted in rats to investigate the toxicity of a series of ADC's. The toxicity was investigated in different tissues (heart, lung, liver, kidney, bone marrow, eye) using histopathology, following administration of vehicle and 3 different dose levels (±5 animals per dose group). The results were summarized per tissue in 5 toxicity scores, ranging from 0 (not toxic) to 5 (very toxic). The proportional odds model was compared to the differential odds model to analyze this categorical data [1]. Furthermore, it was investigated how the model outcome can be used to compare the toxicity of the different compounds.

Results: The proportional odds model was selected to analyze the toxicity scores, since no statistically significant improvement in model fit was observed when using a differential odds model. The toxicity in the different tissues of the different compounds could not be compared using the slope of the exposure-response relationship for toxicity, since the slope was highly dependent on the baseline probabilities of the different scores. The different compounds were compared using EC_{50}'s, which were directly derived from the slope of the drug effect and cumulative probabilities between the cutpoints. The EC_{50x} was defined as the concentration where the probability of score x is reduced by half. Not only the obtained values, but also the distance between them for a compound was found to be informative on its toxicity. The EC_{50x} values of the different compounds were normalized by their tumor static concentrations to derive toxicity scores. Ranking of the compounds according to the obtained toxicity scores gave good correspondence with an external validation method.

Conclusions: A new model-based method was developed to easily assess and compare categorical toxicity scores. This method can be used for rapid screening of ADC's during drug development.

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Adrien Tessier IV-27 Contribution of nonlinear mixed effects models and penalised regression approaches in pharmacogenetic population studies

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Context: Pharmacogenetics is now part of many clinical trials, in particular in population pharmacokinetic/pharmacodynamic (PK/PD) studies. Several methods are available to test the association between PK/PD and genetic covariates which deal with a large number of correlated polymorphisms, but there is no gold standard. In addition, they may be applied to different PK phenotypes, such as PK parameters estimated through noncompartmental analysis (NCA) or NonLinear Mixed Effects Model (NLMEM).

We investigated four association tests; a stepwise procedure and three penalised regressions (ridge regression [1], lasso [2], hyperlasso [3]), applied to four phenotypes; concentrations observed 24 and 192h after dose, area under the curve (AUC) estimated by NCA and PK model parameters estimated by NLMEM (CL, V2 and Q). A simulation study was used to compare the combinations of association tests and phenotypes.

Methods: Simulations used a PK model developed for a compound presenting a nonlinear bioavailability F [4] along with 176 Single Nucleotide Polymorphisms (SNP). Concentrations for 200 data sets were simulated under the null (H_0) and alternative hypothesis (H_1) for several scenarios inspired by real clinical trials, including limited or large number of subjects, and different structural models. All methods were set to target an empirical family wise error rate of 20%. Under H_1, six SNP were drawn randomly and set to affect the elimination of the drug explaining overall 30% of its variability. The number of true and false positives (TP/FP) and the detection probability of the methods were evaluated.

Results: In presence of nonlinearity and/or variability in F, the methods were more powerful to detect a gene effect when applied to a PK model parameter than with other phenotypes. When the PK was linear without variability in F, their behaviour was similar when applied to NCA or PK model phenotypes. All methods were similar in terms of detection probability and showed a low ability to detect genetic effects when the number of subjects was small. Ridge regression had the largest probability to detect SNP, but also a higher number of FP.

Conclusion: Using PK model parameters is a more versatile approach than considering NCA phenotype, with more power to detect a genetic effect except when the PK was simple with a rich design. However, all approaches needed a large number of subjects (approx. 400) to detect a clinically relevant effect, especially with infrequent variants.

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Liping Zhang IV-55 A Mechanistic Modeling Approach Characterizing the Interaction of Pharmacokinetics and Pharmacodynamics of a Monoclonal Antibody and the Supply/Synthesis of its target in Cynomolgus Monkey

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Objectives: To develop a mechanistic PK/PD model simultaneously describing the nonlinear interaction between antibody and its target, including drug disposition, antibody-target binding, target removal, and the hypothesized impact of antibody on the supply/synthesis of the target

Methods: Experimental biological compound, Drug X is a fully human monoclonal antibody designed specifically for binding to a growth factor. Steady state serum concentration data of Drug X and its target in cynomologus monkeys were obtained after weekly subcutaneous dosing of 1x, 3x, 10x, and 50x mg/kg. The concentration of Drug X was approximately linear to dose in the studied regimen. The concentration of drug-target conjugate increased with dose and followed the PK profile of antibody at doses lower than 10x, but for most of the dosing duration at 50x, the conjugate concentration was lower than that of 10x, until substantial amount of antibody was removed from the system after the dosing is stopped. Using NONMEM 7, a targeted-mediated drug disposition (TMDD) model was developed and integrated with a “threshold hypothesis”, in which antibody at concentration higher than a certain threshold reduces the amount of target available for binding; such an effect is gone and fully reversible after the antibody concentration falls below the threshold.

Results: A TMDD model integrated with the threshold hypothesis successfully described the observed concentration profiles of antibody and conjugate at all tested dose regimen. The PK model components included target binding, subsequent degradation, and linear first-order elimination from serum. Target was constantly generated in the system, bound to the antibody, and get cleared from serum either as free target or as antibody-target conjugate. The input rate of target available for antibody binding was not impacted by antibody at doses lower than 10x. At doses above 10x and for the duration of antibody concentration higher than a threshold, the antibody suppressed the supply of target available for binding. Parameters in the model, including the hypothesized threshold value were estimated with good precision. Model-based simulation was performed to predict the full time-course of the antibody, free target, and conjugate at various dose levels and regimen.

Conclusion: By adding one more structure parameter to a typical TMDD model, the “threshold hypothesis” successfully described the unusual antibody-target conjugate profile observed at higher doses. The model may be utilized to predict the time-course of non-quantifiable target profiles and to ascertain the complex interaction between antibody-target binding, abundance of antibody, and the supply/synthesis of target.

Tomoko Freshwater I-07 Competitive landscape model using meta-analysis and simulation-based evaluation for Phase IIb study design of MRL-1 being developed for the treatment of rheumatoid arthritis

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Objectives: 1) To assess a competitive landscape for MRL-1 by comparing with market leaders and key competitors (disease-modifying antirheumatic drugs [DMARDs] and anti-tumour necrosis factor [TNF]) and define relative advantages of MRL-1. 2) To compare different study designs and optimize sample size through a simulation-based approach to provide confidence that the Phase IIb design offers high probability of demonstrating a robust dose-response relationship.

Methods: 1) benchmark efficacy database for the MRL-1 and competitor was created through literature on compounds approved or evaluated for treatment of rheumatoid arthritis. The database included longitudinal summary-level information for efficacy endpoints at different dose levels and patient characteristics (covariates) for 31 drugs (12 used) tested in 88 controlled clinical trials (85 were used) in more than 200,000 patients. The model-based meta-analyses including time course observations for efficacy endpoints, ACR20 and other key endpoints, were conducted using NONMEM and R to characterize the probability that MRL-1 would be greater, similar or worse on efficacy endpoints given uncertainty in the literature by establishing the time course of efficacy endpoints which enabled comparison of onset of action relative to competitors. 2) To optimize Phase IIb design, the evaluation of different sample size and dose options was conducted by integrating the MRL-1 model with key trial design attributes in a clinical trial simulation (CTS).

Results: (1) Based on the competitive landscape modeling, there was a 50 to 70% probability that MRL-1 would be similar or better on the ACR20 efficacy end point vs. all competitors. (2) The exposure-efficacy relationship allowed exploration of alternative dosing regimens and helped us to better characterize different dosing (QD/BID) regimens. The simulations allowed us to define the most efficient sample size and dose arms. CTS was used by MRL-1's project team to guide its design of the next trial.

Conclusions: A comparator model supported the decision to continue with clinical development of MRL-1 based on the efficacy comparison. Further, the modeling efforts were pivotal to select Phase IIb doses and the sample size needed to fully characterize the exposure-response for efficacy parameters.

Marc Gastonguay I-11 Proposal for a Web-Based Open Pharmacometrics Curriculum: Results of a Four-Month Pilot Evaluation

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Objectives: Given the small number of formal academic training programs and associated faculty, resource sharing and collaboration in pharmacometrics (PM) training are critical to the continued development of the discipline [1]. The objectives of this work were: 1). to quantify the extent and intensity of global interest in an open pharmacometrics curriculum (OPC), and 2). to identify additional web-based resources that could potentially make up a complete OPC.

Methods: Six semester-long courses on various PM-specific topics were developed, with audio/video, recordings and supporting example files. The resulting 126 videos were made open and freely available by posting on a YouTube channel [2], with simultaneous announcement on the NMusers discussion group. Usage data from Google web analytics were collected over a 4-month period. Web searches were performed to identify additional open courses, relevant to an OPC.

Results: Over the 4-month period, lectures were viewed 15,240 times, from individuals in 76 different countries, for a total of 129,375 minutes watched. A pattern of short views in the initial week of availability, was followed by a pattern of longer view times (averaging approximately 20 min. each), which was sustained over the time studied. Views primarily originated from computers (88%), followed by tablets (7.6%), and mobile phones (4.4%). 200 individuals subscribed to the channel. Additional freely available, open web courses were identified to supplement the OPC, in topic areas such as: math, pharmacology, programming languages, and statistics.

Conclusions: Results reveal a strong global interest in an OPC, with evidence of in-depth study of the materials, and ready availability of additional training content. Given the positive initial results, future efforts will focus on building a complete OPC.

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Leonid Gibiansky I-15 Numerical Testing of Assumptions for Target-Mediated Drug Disposition (TMDD) Equations: Why Inexact Model Provides Satisfactory Description?

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Background: TMDD equations are based on a number of assumptions such as: 1-to-1 drug-target binding; binding and elimination occur only in the central compartment; target R and drug-target complex RC do not distribute to the peripheral compartment; target production rate k_{syn} and degradation rate k_{deg} do not depend on the drug C or target R concentrations. The real biological systems are unlikely to conform to these assumptions. Yet the TMDD approximations were shown to provide excellent fit of the observed data.

Objectives: To investigate whether the classical TMDD model is able to describe simulated data from biological systems that violate the assumptions of the TMDD equations.

Methods: Dense population data of total drug C_{tot}=C+RC and total target R_{tot}=R+RC concentrations were simulated for the following TMDD models:

M1: standard;

M2: elimination from central and peripheral compartments;

M3: elimination only from the peripheral compartment;

M4: diffusion, binding, and internalization (k_{int}) of R and RC in both compartments;

M5: target production rate k_{syn} dependent on C or R;

M6: target production, binding and elimination in/from the peripheral compartment;

M7: 2 drug binding sites and various values of binding parameters k_{on} and k_{off}.

The quasi-steady state (QSS) approximation of the standard TMDD model was used to fit the data. Model predictions and parameter estimates were compared with true the values.

Results: The QSS approximation provided an excellent fit of the data for all models except M5, where R_{tot} predictions were biased at low R_{tot} values. Most parameter estimates agreed with the true values. The exceptions were (> 25% bias): parameters of the peripheral compartment (Q, V_2) were under-estimated in M2 and M3; clearance (CL) was under-estimated in M3; k_{int} was over-estimated in M4 and M6. CL, Q, V2, and k_{int} were biased in M5 but the fit was improved and bias eliminated when dependencies k_{syn}(C) or k_{syn}(R) were added. QSS constant K_{SS} was in the range of 40%-103% of the true (k_{off}+k_{int})/k_{on} value in M7.

Conclusions: QSS approximation of the standard TMDD model can be used to describe TMDD system even if underlying assumptions are not met by the true system. The fit was most sensitive to perturbations of the target production rate.

Anais Glatard I-17 A model-based approach to support NOAEL determination: a simulation case illustrated by a real dataset

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Objectives: In drug development, a "no observed adverse-effect level" (NOAEL) is derived from animal studies and used to infer a maximal safe exposure in human[1,2]. The current practice is to determine NOAEL for first-time-in-human studies on the basis of discrete observations from pivotal toxicity studies, which are limited by specific experimental conditions. We hypothesise that this practice may not represent the optimal use of data, and may carry a risk of misrepresenting the true NOAEL[3-6]. We propose to explore by simulations a model-based approach in complement to the current practice. A real case was used to illustrate the simulation findings.

Methods: A linear logit model including i) background toxicity incidence, ii) study duration effect and iii) dose effect was used to simulate a dose-toxicity probability pattern of relevant toxicity experimental settings. Different scenarios in terms of sample size per dose group, level and number of doses and degree of drug toxicity were considered to investigate the NOAEL distribution. For each scenario, 1000 replicates of individual binary toxicity effects (presence/absence) were simulated. NOAEL was defined as the next dose level down from the dose group wherein the toxicity frequency was higher than in the concurrent control group. A real life example was used to illustrate the model-based approach to support NOAEL determination using histopathological data from 7 rat toxicity studies.

Results: The simulations showed that higher sample size or higher number of doses tends to lower NOAEL doses. In the case of a drug with flat dose-response, the NOAEL dose lower than the lowest dose is selected as frequently as the highest dose. The modelling of real data allowed characterisation of the dose-toxicity probability relationship for the example drug across studies. The NOAEL doses derived by current practice from each study could be then graphically linked to the true model-based toxicity probability

Conclusions: A model-based approach allows a quantitative characterisation of the toxicity frequency as a function of any dose (even those not tested) integrating treatment duration and uncertainty due to sample size. The simulations illustrated an issue associated with the current approach in defining and estimating NOAEL: NOAEL tends towards the lowest doses studied and this tendency is higher with larger sample size. These findings suggest that a probability-based approach might be a more robust alternative.

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Marta Gonzalez I-19 In-silico Biopharmaceutical Systems for Provisional Classification of Oral Drugs

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Classification of drug candidates based on the Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS) has become an important issue in pharmaceutical researches [1, 2].

Objectives: The main goal of the study was to develop robust *in-silico* models to classify the solubility, permeability and metabolism properties that define both systems, allowing the definition of a new computational biopharmaceutical filter. The modeling approach for BCS/BDDCS combination is an unexplored area with high relevance for application in both new drug screening and in later drug development stages.

Methods: Three extensive and heterogeneous databases (solubility, permeability and extent of metabolism) and three machine-learning techniques (support vector machine, kappa nearest neighbor and multilayer perceptrons) were used to develop QSPR classification models.

Results: Nine single classification models were selected and three voting systems were constructed. The final consensus models had global accuracies greater than 82% for each property. The *in-silico* BCS was validated with a dataset of 139 compounds classified by WHO and the *in-silico* BDDCS was assessed with external dataset of 131 compounds. In the first case, the models correctly classifies 88.4% of class I drugs, 78.3% of class II drugs, 76.6% of class III drugs and 80.8% of class IV drugs. Likewise, the *in-silico* BDDCS system correctly classifies 78.7% of class I drugs, 80.0% of class II drugs, 87.9% of class III drugs, and 71.4% of class IV drugs. On the basis of both *in-silico* BCS/BDDCS systems was defined a biopharmaceutical filter that includes eight possible outputs of drugs, drug-like molecules or NMEs.

Conclusions: The results fairly demonstrated the validity of *in-silico* biopharmaceutical systems for provisional classification of oral drugs in early drug development process.

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Isabel Gonzalez-Alvarez I-22 Semi-physiologic model validation and bioequivalence trials simulation to select the best analyte for acetylsalicylic acid

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Due to the different criteria of the European and American Guidelines for bioequivalence, our investigation group had studied theoretical drugs with different kind of metabolism, to define the most sensitive analyte (parent compound or metabolites) for in vivo bioequivalence studies.
In this work we studied a drug with first-pass hepatic and intestinal metabolism and Michaelis-Menten kinetics that lead to the formation of two main metabolites in two generations (first and second generation metabolites).

Objectives:1) to present a semi-physiological model for acetylsalicylic acid (ASA), 2) to validate the model and 3) to determine which analyte (parent drug, first generation or second generation metabolite) was more sensitive to changes in the dissolution constant (K_D) of the formulation.

Methods:A semi-physiological model was proposed to represent this pharmacokinetic behavior. The chosen compound was the acetylsalicylic acid (ASA). The semi-physiological model was developed in NONMEM VI using ASA parameters from bibliography. The first aim was to present a semi-physiological model for ASA, showing its sequential metabolism. The second aim was to validate this model to know if it represents the ASA behavior. The validation was made comparing the results obtained in NONMEM simulations with published experimental data at a dose of 1000mg. The validated model was used to simulate bioequivalence trials at 3 dose schemes (100, 1000 and 3000mg) and at 6 decreasing *in vivo* dissolution rate constants of the test formulations (k_D 8 to 0.25h^{-1}) to achieve the third aim of the study: to determine which analyte (parent drug, first generation or second generation metabolite) was more sensitive to changes in the formulations performance.

Results: The validation results showed that the concentration-time curves obtained with the simulations fitted the published experimental data, so we consider that the model is validated. The bioequivalence results showed that the parent drug was the most sensitive analyte for bioequivalence trials. The parent drug (ASA) was the first analyte that showed a great decrease in Cmax ratio between test and reference formulation. In addition, in most scenarios the parent drug was the first analyte that showed a decrease in AUC ratio. The exception to this occurred at doses of 1000 and 3000mg when k_D was 0.25h^{-1}: in these two cases, the AUC ratio of the first metabolite (salicylic acid) was a little bit lower than the ratio of ASA.

Conclusions:1) The proposed model was considered validated. 2) The parent compound (ASA) was more sensitive than its main metabolites (SA and SU) to changes in the K_D of formulations.

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Garrit Jentsch I-40 The BAST Clinical Trial Simulator: A computational framework for quantitative risk assessment.

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Objectives: Recent years have witnessed the emergence of various Model Based Drug Development (MBDD) strategies all of which centre around a continuum of mathematical statistical models that capture the developing project from the patho-physiology of the disease and the pharmacology of the drug to the conduct of clinical studies. The model continuum is maintained to simulate experiments and clinical studies in order to optimise their design and to quantitatively assess their chance of success.

Methods: Computational frameworks supporting a MBDD strategy are very rare. We have started to develop an agent-based simulation environment that allows us to integrate the model continuum in a single framework. The first prototype evaluates the operating characteristics of a simulated trial. The underlying statistical models are formulated in NMTRAN (ADVAN13) but simulations are executed without the use of NONMEM.

Results: Two case studies are presented. The first study demonstrates the use of the clinical trial simulator (CTS) from the perspective of a payer assessing a new treatment by evaluating whether a randomly selected subject from an active treatment group experiences a response that marks an improvement over the response of a randomly selected subject from a control group. The target is set at improvement in 85% of the cases. A biomarker indicative of disease severity is simulated, and a probability of achieving the target value (PTV) of 0.9 is determined.

The second case study deals with the development of a new drug against a disease whose severity is measured by a composite score. Using data of a phase II trial the CTS is used to identify the dose level and observation period that should be used in a confirmatory trial. Treatment is successful, if 50% of the patients exhibit a disease score lying below a certain threshold. The outcome of each simulated trial is evaluated with a proportion z-test at a significance level of 0.05. Simulations reveal that only one of the proposed dose levels leads to a PTV > 0.8. In order for the probability of success of the trial to approach the PTV more than 500 subjects would need to be studied.

Conclusions: The case studies demonstrate how the CTS evaluates the operating characteristics and success chances of a clinical trial and how it guides study design optimisation.

Irene-Ariadne Kechagia I-49 A meta-analysis methodology to estimate population pharmacokinetic parameters from reported non-compartmental values with sparse sampling

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Objectives: To develop and assess the performance of a meta-analysis method to estimate the population pharmacokinetic parameters with the respective interindividual variabilities (IIV) from reported non-compartmental parameter values (NCP), taking into account the sampling schedule that was used to calculate the latter.

Methods: A structural model was constructed to calculate the NCPs, namely Cmax, AUC, tmax and $t_{1/2}$. Unlike other methods [1, 2] in which the NCPs are calculated according to theoretical formulas, here they are calculated exactly as reported. Using a one-compartment model with first order absorption, the concentrations at specific sampling time points are simulated. Cmax and tmax are the maximum of these concentrations and the respective time, $t_{1/2}$ is calculated from the slope of the log transformed three last points and AUC by the trapezoidal rule and extrapolation to infinity. A two stage approach is applied to estimate the compartmental parameters (CP), CL, V and ka. Initially, geometric means of the NCPs, namely Cmax, AUC and $t_{1/2}$, are used to estimate population means of the CP. Interstudy variability is also included as random effects to account for random variability of the different reported NCPs from which covariates can be determined. At a second stage, coefficients of variation (CV) of the NCPs, namely Cmax, AUC, tmax and $t_{1/2}$, are calculated by Monte Carlo sampling and used to estimate the IIV of the CP. Estimation was performed with the FOCE method in NONMEM V7.2.0 using a custom written Fortran subroutine for the PRED. To evaluate the performance of the method simulations were carried out. The method was applied to develop a PopPK model for valaciclovir administered to paediatric population [3].

Results: The relative bias in the population parameters (IIV), CL, V and ka, was -1.5% (-5.0%), 3.8% (-10.3%) and 7.5% (21.4 %) respectively. The respective RMSE was 1.7% (13.6), 3.8% (17.3 %) and 8.7 % (36.3 %). The results show that the method is capable of estimating the population means with satisfactory bias and precision, while the variances exhibit higher but acceptable imprecision. A paediatric PopPK model for valaciclovir was developed having age as a covariate on CL and V.

Conclusions: The method can cancel out the bias of the NCP values introduced by the relatively sparse sampling, by taking into account the exact way these were calculated in the first place and thus develop a population pharmacokinetic model from the NCPs, particularly applicable to paediatric sparse data.

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William Knebel I-55 Elastic Cloud Computing in Pharmacometrics: Usage Data and Strategies for Efficient Workflows

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Objectives: In theory, elastic cloud computing (EC2) could virtually remove computing time from the critical path of pharmacometric (PM) projects. Optimization of the relationships between available EC2 resources, modeling strategies, and scientist teams, will be required to achieve the full performance potential. The objectives of this work were to capture the usage patterns for a typical group of modeling and simulation (M&S) scientists, and to summarize strategies for effective use of EC2 resources for PM analyses.

Methods: Usage patterns, based on the number of simultaneous compute cores (SCC) utilized, for a group of M&S scientists with access to Amazon EC2 based virtual machines, were captured to assess sustained and peak use of cloud based resources over a 6 month period. SCC usage reflected a combination of NONMEM(R), R, and/or OpenBUGS software. Actual usage patterns for a group of 14 individual users were recorded. These data were used to simulate via resampling, the usage patterns for groups of up to 64 users. A strategy for efficient EC2 resource utilization was also illustrated by summarizing an actual PM project. This case-study included population model development for 3 endpoints requiring numerical integration of differential equations and simulation-based evaluation of Phase 2 and 3 trial designs options.

Results: The most active user over the 6 month period demonstrated multiple usage peaks of 150 SCC, with several days of less than 10 SCC. For the group of 14 users, peak usage of 750 SCC was demonstrated on a single day with sustained usage of 250 SCC over the 6 month period. Simulation of the group of 64 users revealed sustained usage of 1500 SCC with intermittent peaks of 2400 SCC over 6 months. For the case study, a strategy of parallel task and computation implementation across a team of 6 M&S scientists, and the EC2 infrastructure, allowed project completion within 14 days, where linear sequential task implementation with a single scientist and EC2 would have required 8 weeks, and linear sequential implementation without EC2 would have required 4 months or more.

Conclusions: Usage of EC2 resources, and associated software, was proportional to the number of users, not maximum number of available cores. Team-based project strategies, with parallel task and computation implementation, maximize the potential utility of EC2 for PM workflows.

Andreas Lindauer II-14 A tool for First-in-human PK Prediction Incorporating Experimental Uncertainty

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Objectives: To develop a user-friendly application that facilitates the routine prediction of human PK with uncertainty on the basis of preclinical data measured with error.

Methods: Recommended methods for human PK predictions at Merck are being refined to more systematically incorporate experimental uncertainty. Equations for first-in-human PK predictions (e.g. well-stirred liver model, allometric scaling of volume of distribution) were coded in R-scripts (R v3.0.2). To conveniently enter experimental data for users not familiar with R, a graphical user interface (GUI) was developed in ASP.NET MVC 4 framework as a front-end. Information exchange between the GUI and R is handled via XML files.

Results: Depending on the type of parameter, the preclinical data can be entered in different formats such as geometric mean and standard error of the measurement or as typical estimate and correlation matrix in case of in vivo PK parameters obtained from fitting a compartmental model to animal data. Upon execution of the R-scripts in the background, random samples are drawn from a distribution determined by the input format (e.g. log-normal, multivariate-normal). In case of parameters that are bound between values of 0 and 1 (e.g. fraction unbound) samples are drawn from a logistic distribution. The equations for preclinical-to-clinical extrapolation are then applied on these sets of random values to predict the distribution of human PK parameters (i.e. bioavailability, volume of distribution, clearance). Simulations of the expected concentration-time profiles are automatically conducted to determine the likelihood of achieving a target concentration (e.g. trough level, AUC; provided by the user) for a range of different doses. The results are visualized as PK curves with confidence intervals, bar-plots displaying the probability of exceeding the target at different doses, and a tornado plot showing the contribution of each input parameter to the overall uncertainty of the prediction of the PK parameter of interest.

Conclusions: Accounting for experimental uncertainty facilitates a transparent team discussion around confidence associated with human predictions. Instead of obtaining a prediction of 'the' efficacious dose, a probabilistic statement can be made about the likelihood that a certain dose will hit the target.
Importantly, from the tornado plots it is immediately visible which parameters are most influential and may require additional experiments to improve the precision of the predictions.

Renhua Zheng II-54 Population Compartmental approaches in bioequivalence studies

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Objectives: The objective of this study is to evaluate the relative performance of population compartmental method vs NCA (non-compartmental analysis) approach in estimating the systemic exposures of drugs in BE (bioequivalence) studies.

Methods: Three BE study data were used for the comparison of population method vs NCA approach. The systemic exposures (C_{max}, AUC) were calculated using the individual post hoc parameters of compartmental PK model from NONMEM®. The same systemic exposures were calculated using the NCA approach implemented in Phoenix® WinNonlin® 6.1. The results from the both methods were compared using geometric mean ratios of test/reference with 90% confidence intervals.

Results: The individual post hoc pharmacokinetic parameters along with the population parameters were estimated by NONMEM® using various sample sizes by resampling the data of the BE studies. The systemic exposures calculated from these pharmacokinetic parameters were similar between the test and reference formulations as based on the geometric mean ratios with 90% confidence intervals. Also, these exposures were comparable to those from non-compartmental methods.

Conclusions: These results indicate that the population modeling approach could be an alternative method for the bioequivalent assessment.

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Sebastien Bihorel III-17 KIWI: a collaborative platform for modeling and simulation

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Objectives: Drug development programs rely increasingly on pharmacometric analysis to support decision-making and submissions to regulatory agencies[1,2]. To ensure high quality analysis, organizations must apply state-of-the-art science and implement a comprehensive infrastructure of procedures, workflows, and informatics capable of efficiently organizing, processing, maintaining, and communicating the volume of data and results generated by pharmacometric departments over the duration of a development program[3,4]. KIWI is a novel platform designed to meet these challenges.
Methods: A cloud-based application was developed as a model development platform for global teams to work and communicate results within a shared and consistently organized workspace. This validated platform allows 24/7 secure data access via web browser. It leverages the power of computational grid environments and facilitates the use of NONMEM, Perl-speaks-NONMEM, covariate search methods, and high-quality R-based diagnostic plotting.
Results: Users interact with KIWI through web modules. WORKBENCH organizes the workspace and implements a permission system defining user access to datasets and model results. It provides tools to manage datasets and control files and to submit jobs to a validated grid environment. MANAGE reports the list and history of completed runs and allows comparison of run results. SUMMARIZE automatically computes customizable summary statistics. VISUALIZE provides users with limited or no knowledge of R tools to create and view customizable diagnostic plots for estimation or visual predictive check runs. ANALYZE provides tools to facilitate covariate searches using stepwise forward/backward methods or generalized additive model analysis. All modules generate formatted outputs for export into technical documents.
KIWI accelerates modeling projects by decreasing the need for custom statistical or graphical code and eliminating quality checks of exported tables and plots. Finally, the validated workflow and tools promote traceability and reproducibility of results and reduce data manipulation errors.
Conclusions: As an integral part of an ongoing effort to enhance cross-department team collaboration and systematize the modeling and simulation workflow, KIWI was developed as an intuitive cloud-based platform for pharmacometrics designed to meet the demands of global teams.

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Sameer Doshi III-56 Assessing the Influence of the Log-Transform Both Sides (LTBS) Approach on the Type 1 and Type 2 Error Rates for Clearance Estimation when using Bayesian Priors

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Objectives: Analyzing pharmacokinetic (PK) data from small numbers of subjects can be supported by the use of Bayesian priors in NONMEM. Bayesian priors may be considered instead of combining the original and new datasets either for speed of the analysis or when the original data are not available to be combined. This simulation study assessed the influence of the LTBS approach on the type 1 and 2 error rates of clearance estimation when using Bayesian priors.

Methods: An open 2-compartment PK model with linear elimination from the central compartment for a hypothetical biological compound was employed to describe the time course of drug concentrations after intravenous bolus, zero order subcutaneous input was employed to characterize drug absorption. Clearance (CL) and volumes were allometrically scaled. Interindividual variability on parameters was set to 25% and the residual error was defined as 20% CCV. Body weights were randomly drawn from the NHANES dataset (http://www.cdc.gov/nchs/nhanes.htm). Plasma drug concentrations were simulated (500 replicates) for two scenarios: 1) subjects with 1x the prior CL and 2) subjects with 1.4x the prior CL. Each replicate consisted of 15 subjects with 8 optimal samples per subject. Profiles were fit with NONMEM 7 using PK priors and with or without the LTBS approach. The probability of observing Type 1 and 2 errors, bias/precision of parameter estimates, and diagnostic plots were evaluated across the scenarios.

Results: Using an exponential error model (non-LTBS), the type 1 error rate was greater than 70% (1xCL). In the same scenario using the LTBS approach, the type 1 error dropped to less than 5%. Type 2 error (1.4xCL) was greater than 20% with non-LTBS and less than 1% with LTBS. With the LTBS approach the estimation of clearance was accurate and precise, while without the LTBS approach the estimation of clearance was inaccurate and imprecise. Overall, the LTBS approach dramatically improved the model fit and the normality of weighted residuals provided an indication of the benefit of the LTBS approach.

Conclusions: The type 1 and 2 error rates as well as the accuracy and precision of clearance estimation using Bayesian priors and LTBS approach is a suitable method for PK data analysis of compounds that follow a two compartment linear PK model with zero order absorption. Further research is ongoing in order to generalize these findings to other common PK models.

Tarjinder Sahota IV-02 Interactive population PK/PD model simulations in R

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Objectives: Simulation from population PK/PD models enables us to quantitatively assess the clinical implications of untested pharmacological hypotheses and intervention strategies. In strategic drug development meetings, real time production of graphical outputs enables evidence based scenario planning where the breadth of clinical team expertise can be leveraged. Traditionally, this has been difficult to do due to software limitations software. The desired workflow should have:

1) Access to a fast and reliable differential equation (DE) solver
2) Functionality for mixed effects models
3) Functionality for complex dosing inputs
4) High quality graphical output with easy widget creation
5) Fast run time

The R language is widely used by PK/PD modellers. Recent package development has provided user friendly access to existing DE solver libraries. RStudio, an integrated development environment for R, also includes a user friendly package for interactivity [2]. The objective here is to illustrate the use of these packages in RStudio for real time interactive PK/PD simulations.

Methods: The following R packages were installed on a standard laptop (Intel Core i5 – 3427U @ 1.8 Ghz, 4GB RAM): deSolve [1], manipulate (installed with Rstudio), and plyr.
The “deSolve” package provides an interface to the Fortran LSODA function. The option to pre-compile enables fast solution of ODEs and an interface is provided for bolus and zero order input into compartments. “plyr” and “ggplot2” provide user friendly data manipulation and plotting capabilities. The “manipulate” package provides functionality to add sliders, checkboxes and menus to plots in Rstudio. We show example interactive output with full source code.

Results: We illustrate an interactive simulation from a population PK model with less than 60 lines of R code. We also show a simulation of a cell life cycle model with delayed differential equations. Speed of execution was predominantly limited by the ODE solver. Specification of ODEs in C++ for compilation drastically reduced run time by more than 10 fold.

Conclusions: The combined use of “deSolve” and “manipulate” packages in Rstudio enables the production of high quality, interactive graphical outputs from PK/PD simulations.

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Satoshi Shoji IV-11 Evaluation of information of prior relative to current data in analysis with prior

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Objectives: When a population of interest is small or data in the population is sparse due to practical constraints, it is occasionally difficult to fit a model with the current data alone. Use of prior [1] is one of the ways to analyze such limited data while borrowing information from the prior and stabilizing the parameter estimation. In this work, we evaluate information of prior relative to current data when analyzing data in a small population or sparse data.

Methods: In this work, information of prior relative to current data is defined as how many times the prior has the amount of information in comparison with current data. This idea was based on prior information of Bayes estimator [2]. To measure the relative information, we use following variance of the parameter estimate.
- $V_{+p}[\vartheta]$ obtained from information of current data + prior
- $V_{+N}[\vartheta]$ obtained from information of current data + N·current data

where ϑ represents a parameter estimate obtained from an analysis with a prior. When $V_{+p}[\vartheta]$ is equal to $V_{+N}[\vartheta]$, information from the prior is considered equivalent to that from the N·current data. We define the N as a scale for information of the prior. We analyzed simulated data of several examples for dose-response in a small population and sparse PK data using frequentist prior of NONMEM $PRIOR [1] to obtain $V_{+p}[\vartheta]$. The N at $V_{+N}[\vartheta]$ equivalent to $V_{+p}[\vartheta]$ was calculated from fisher information matrix of parameter estimates [3] given the estimate ϑ and current study design.

Results: When the information of prior was small (e.g. N around 1 - 2), the parameter estimate was governed by the current data as well as the prior. In those cases, even when the prior was misspecified, the parameter estimate was little influenced by the misspecification. In the meanwhile, in extreme cases of large prior information (e.g. $N > 30$), as expected, the parameter estimate was mostly governed by the prior, resulting in little improvement in the estimation bias when the prior was misspecified.

Conclusion: Parameter estimates obtained by use of the priors could be applied to infer a population of the current data, depending on information of the priors and the current data. Although further investigation and improvement is needed, information of prior relative to current data presented in this work may be used as one of the scales.

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Kabir Soeny IV-13 A Novel Algorithm for Optimizing Dose Regimens and Fixed Dose Combination Ratios

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Objectives: Nowadays, regulatory authorities actively challenge the dose regimens suggested by the industry, usually by stating that the doses are unnecessarily high and leave the burden of proof with the company applying for the approval [1]. The dose regimen which minimizes the under- and over-exposure around the target concentration maximizes efficacy and safety, resulting in increased chances of a successful approval. For some indications (HIV, Malaria, Tuberculosis), combination therapies are mandatory to prevent the spread and/or development of resistance to the single components of the regimen and should be enforced. Therefore, it is crucial that the optimal dose ratio has been identified during the development process and has been taken forward for approval. In this paper we present a novel algorithm for optimization of loading and maintenance doses of single drugs and its extension to include the optimization of the ratio of drugs for a fixed dose combination.

We developed a general theory for dose regimens which minimize the under-and over-exposure around the target concentration. We developed the 'Efficient Dosing algorithm' (programmed in MatLab) for computation of such dose regimens. It is an iterative algorithm such that in each iteration, the dose regimen at the current iteration moves towards the optimum dose regimen. The algorithm converges when no further minimization is possible. We extend the algorithm for the case of combination therapies such that we determine not only the optimum dose regimen to be followed, but also the optimum ratio in which the drugs should be mixed in a dosing unit.

We applied our algorithm on the anti-malarial drug Coartem. Coartem is made up of Artemether and Lumefantrine in the ratio of 1:6. We applied our algorithm to optimize the dose regimen and the combination ratio. We found a dose regimen and a combination ratio which could be 40% more efficient than the ones currently used. We took the pharmacokinetic parameters of the drug from [2] and [3] and assumed the targets to be 50% and 75% of the maximum concentration achieved by Artemether and Lumefantrine respectively.

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Sebastian Ueckert IV-31 Accelerating Monte-Carlo Power Studies through Parametric Power Estimation

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Objectives: To evaluate the performance of a novel algorithm for faster sample size calculations and compare it to sample size calculations through standard Monte-Carlo simulations and estimations.

Methods: Power versus sample size curves for 3 different pharmacometric models (disease progression, PK auto-induction and count) were calculated with 2 different methods: (i) an algorithm using pure Monte-Carlo simulations and estimations (MC) and (ii) a novel parametric power estimation (PPE) algorithm. All calculations were repeated for a differing number of Monte-Carlo samples (100, 200, 300, 400 and 500) and the power estimates from both algorithms were evaluated for accuracy and precision. Power estimates obtained with the MC algorithm and 10,000 Monte-Carlo samples served as a reference.

MC algorithm: For each sample size, N datasets are simulated, re-estimated with a full and reduced model and the log-likelihood ratio test is carried out. The power estimate for a specific sample size is the number of dataset where the null hypothesis was rejected.

PPE algorithm: For a complete power versus sample size curve, N dataset are simulated and re-estimated with full and reduced model. The resulting N log-likelihood ratios are used to estimate the non-centrality parameter of the theoretical non-central chi-square distribution [1] and the power for a specific sample size is determined from the cumulative distribution function. Simple scaling of the non-centrality parameter yields the full power curve.

Results: For all 3 examples investigated the median power estimates from both algorithms were in good agreement with the reference. However, the power estimates from the PPE algorithm displayed a small bias between 0 and minus 2%.

For one sample size the PPE algorithm required about 50% fewer Monte-Carlo samples to achieve the same precision of the power estimates. More importantly, the full power versus sample size curve was derived from one single non-centrality parameter estimate. Thus, compared to a power curve calculated with the MC algorithm at 8 grid points, the PPE algorithm reduces the number of required Monte-Carlo samples by a factor of 16.

Conclusions: The PPE algorithm can obtain full power versus sample size curves with drastically reduced computational effort than through pure Monte-Carlo simulations and estimations.

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Ana Kalezic I-45 Sample size calculations in multiple sclerosis using pharmacometrics methodology: comparison of a composite score continuous modeling and Item Response Theory approach

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Objectives: Clinical trials in multiple sclerosis (MS) therapeutic area are particularly long due to the variable and slowly progressive nature of the disease. Phase III trials are often conducted for over two years and frequently include more than a thousand patients. Therefore, increased efficiency would be valuable. This analysis aims to demonstrate the application of pharmacometric methods for power/sample size calculation based on Expanded Disability Status Score (EDSS) [1], a widely used measure of disease disability in MS, as efficacy endpoint.

Methods: Clinical trial simulations were used to compare the power to detect the drug effect for two Non-Linear Mixed Effect (NLME) models previously developed for EDSS. One is treating EDSS as a continuous, composite variable [2] and the second one is using Item Response Theory (IRT) methodology [3]. The IRT model was used for simulations according to predefined study design. Study design was a 96-week Phase III clinical study with relapsing-remitting MS, where patients received active treatment or placebo, and EDSS assessment was conducted every 12 weeks during the study. These scenarios were explored: that the drug has both offset and disease modifying effects or one of these alone.

The simulated data were subsequently analyzed using a continuous composite and an IRT model. The power calculations were performed using Monte Carlo Mapped Power method [4], implemented in PsN software. All simulations were performed and models fitted using NONMEM 7.2.

Results: In the current example, we show that using the IRT model requires 81 patients, compared to 131 with a continuous composite model to achieve 80% power to detect a dual drug effect. It represents 40% reduction in sample size. In case of offset and disease modifying drug effect alone, 20% and 40% fewer patients were necessary using IRT model, respectively.

Conclusions: Taking a model-based approach offers an opportunity to gain efficiency in clinical trials. In the current example, the IRT model indicated overall a need for lower sample size to detect the drug effect compared to continuous composite model regardless whether the drug effect was an offset, disease modifying, or both.

This is in line with previous findings that IRT increases precision in predictions and power to detect drug effects and linkage to biomarkers [5, 6]. Therefore, these NLME models could be used as a support for MS clinical trials design and analysis.

Acknowledgement: This work was supported by the DDMoRe project.

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Giulia Lestini II-11 Two-stage adaptive designs in nonlinear mixed-effects model: an evaluation by simulation for a pharmacokinetics (PK) and pharmacodynamics (PD) model in oncology

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Objectives: Optimal design in population PKPD is based on prior information on the models and on the parameters. Adaptive designs [1,2] are a promising alternative to local or robust designs [3] . Two-stage designs are easier to implement than fully adaptive designs and can be as efficient [4]. Here, we compared by simulation one and two-stage designs using a PKPD model in oncology.

Methods: The PKPD model is the one developed for a TGF-β inhibitor [5]. We assumed that the model is known, and we defined two set of population parameters. A priori wrong values of the parameters, Ψ^0, were obtained after an animal study and human scaled allometry as in [5]. "True" parameters, Ψ^*, are those obtained in an clinical study [6].

We considered various designs with a total of N=50 patients with the same elementary design ξ in all patients within the same cohort (i.e. the same stage). We first consider a rich design ξ_{rich} with 6 sampling times. We then optimized various sparse design with 3 samples: i) ξ^0 optimized with Ψ^0, ii) ξ^*optimized with Ψ^*, iii) two-stage designs that combined N_1=25 patients in first cohort with design ξ^0 and N_2=25 patients in second cohort with design ξ^2, where ξ^2 was optimized after the results of the first stage. Design optimization was performed using determinant of the Fisher Information Matrix (FIM) using PFIM 4.0 [7]. For the two-stage design prior information obtained after first stage was incorporated in the evaluation of FIM.

We simulated 100 datasets for each scenario using true parameters Ψ^*. Parameters were then estimated using the SAEM algorithm in MONOLIX 4.3. Relative Bias (RB) and Relative Root Mean Square Error (RRMSE) were used to compare the various designs.

Results: RB and RRMSE were relatively small for designs ξ_{rich} and ξ^*, whereas they were rather large with the design ξ^0, showing first the importance of the prior parameters in the optimization of the design and second the poor performance of the design if the choice is wrong. For the two-stage design we obtained results close to the one-stage design, ξ^*, showing the ability of the two-stage design to correct the design after the first cohort.

Conclusions: With a two-stage design, results are very close to those of the one-stage design using true prior parameters and are much better than those using wrong prior parameter. Study on the best balance between sizes of each cohort is ongoing.

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France Mentré II-22 PFIM 4.0: new features for optimal design in nonlinear mixed effects models using R

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Objectives: To extend PFIM, the only tool for population optimal design in R, with several new features.

Methods: Model based optimal design approaches are increasingly used in population pharmacokinetic/ pharmacodynamics (PKPD) [1]. These approaches rely on the Fisher information matrix (FIM) for nonlinear mixed effect models and are a good alternative to clinical trial simulation. Several software tools are available and were recently compared [2]. They all incorporate a PKPD library of models and model defined by differential equations. PFIM (www.pfim.biostat.fr) is available since 2001 and was extended in version 3 to multi-response models, inter-occasion variability, discrete covariates with prediction of power of Wald test [3].

We released in spring 2014 the version 4 of PFIM with several new features that we applied on several PKPD examples.

Results: For population designs, optimization can be done with fixed parameters or fixed sampling times. Previous information already obtained can be assumed and loaded through a predicted or an observed FIM. This is crucial to performed adaptive designs which are a strong requirement in drug industry and one of the task of the DDMoRe project [4].

Additional features for design in Bayesian estimation of individual parameters were added. The Bayesian information matrix was implemented. Design for MAP can be evaluated or optimized [5]. The predicted shrinkage is also reported [5]. We show with various examples the influence of design on shrinkage. This is a useful feature to select informative sampling times in therapeutic drug monitoring.

Conclusions: This new version of PFIM fulfilled some of the needs expressed in industry [1]. The examples again showed the importance of model based optimal design to predict good studies and anticipate 'fatal' ones.

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Claire Ambery III-05 Bayesian bio-comparability using small sample sizes and quantification of safety risk

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Objectives: A test compound is being developed as a potential oral anti-inflammatory. The compound will be investigated for the first time in patients in a long term study. However the tablet manufacturing process for the compound has been modified, and although in vitro data indicates the tablets should perform similarly, given the study duration and known variable PK profile it was considered prudent to perform an interim PK check to de-risk the long term trial. As a first proposal an interim PK assessment was proposed in 16 subjects. The objectives of this work were to determine the minimum number of patients required to give sufficient confidence that exposure is unchanged, the minimum number of patients required to give confidence to dose adjust and to quantify the risk of potential PK exposure changes ahead of study start.

Methods: PK exposure data from 30 healthy subjects was used to calculate the posterior distribution for the PK parameters of interest. The posterior probability that the 'True' exposure is within criteria of interest (<0.8, 0.8<x<1.25,>1.25) was determined for a range of potential observed ratios (0.333x to 3x) and sample sizes (N = 2n-1, with n = 1 to 6). The operating characteristics of our decision rule for dose adjust (rule out two-fold change in PK exposure) were determined by simulation to quantify how often a dose adjustment would be proposed if in truth exposure was unchanged. The probability of exceeding PK exposure limits was determined for a range of potential PK changes.

Results: If the true ratio (test-patient/reference-healthy) is 1, i.e. the distribution is the same in both groups, then 8 subjects would provide the team with sufficient confidence they would make the dose adjustment an acceptable percentage of the time. Whereas, if there is great disparity between the groups, very little data is required. For a sample size of 8, if the true ratio (test/reference) is 1, then less than 5% of simulated studies would require dose adjustment. If the true reduction is 20% (ratio = 0.8) then for a sample size of 8 subjects 30% of studies would result in dose adjustment. The probability of exceeding the safety limit in a future subject if the PK exposure is unchanged is 0.11%. The probability of exceeding the safety limit if PK exposure is 50% increased is 8.6%.

Conclusions: By utilising Bayesian decision theory the sample size to provide sufficient confidence to rule out a two-fold change in PK exposure compared with historic data was half that typically studied. Safety risk ahead of study start was quantified.

Charlotte Barker III-11 Synthesising pragmatic and optimal design: NAPPA - a paediatric penicillin population pharmacokinetic study

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Objectives: The Neonatal and Paediatric Pharmacokinetics (PK) of Antimicrobials study, NAPPA, is a multicentre population PK study evaluating six penicillins used in routine care (amoxicillin/ampicillin/benzylpenicillin/coamoxiclav/flucloxacillin/piptazobactam). The protocol uses opportunistic ('scavenged') sampling strategies, which can be supplemented by optimally timed samples using a non-invasive method (e.g. arterial catheter sampling). The NAPPA optimal design strategy aimed to identify optimum timing recommendations grouped across all participant age-groups, from infants to adolescents.

Methods: The optimal design exercise was implemented with PopED software using the D-optimality criterion. A literature search was first undertaken to identify published population PK models of the relevant penicillins in order to select an appropriate model on which to base the optimal design. Modelled participants' ages were allocated to the mid-point of each age-group, linked with mean weight-for-age. A representative dosing strategy was selected: single intravenous flucloxacillin bolus of 25mg/kg. Participant number per group was set at the maximum study target. The additive residual error was adjusted to reflect anticipated assay limits: 2.5mg/L. Three optimal sampling times were predicted. Sampling windows were identified to increase the feasibility of sampling in routine healthcare.

Results: A three compartment PK model based on flucloxacillin PK data was selected from the literature [1]. A maturation function was added to the clearance parameter [2], to account for changes relating to age and weight:
CLA = CL*(Weight/70)^0.75*(Age^3.4/(47.7^3.4+Age^3.4))
The D-optimal design results were as follows, with the associated sampling windows selected:

Sample number	1	2	3
Optimal time (hours post dose)	0.26	1.67	3.54
Sample window	0.17-0.50	1.42-2.25	3.00-4.00

The impact of these sampling windows resulted in 84% normalized efficiency.

Conclusions: D-optimality design in PopED was used to select optimal timing recommendations for a penicillin PK study in different age-groups, from infants to adolescents. The feasibility of the recommendations was enhanced by selecting practical timing windows to reflect the flexibility needed in routine healthcare for study implementation. Future work will consider whether the recruitment targets within different age-groups can be adjusted to reflect the maturation of clearance associated with changes in age and weight over time.

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Ari Brekkan Viggosson III-22 Optimized Reduced Designs of Pharmacokinetic Clinical Trials Utilizing Target Mediated Drug Disposition Models

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Objectives: Monoclonal antibodies (mAbs) may display target mediated drug disposition (TMDD) [1] when target binding notably alters the disposition of the drug. In this work TMDD models, combined with optimal design methods, were employed to evaluate the consequences of reduced sampling designs for mAbs. The aim was to i) optimize reduced sampling schedules for TMDD models and ii) determine the consequences of reduced designs on parameter precision, precision of free target level predictions at certain time-points and on dose choice for future studies.

Methods: The quasi steady-state (QSS) and quasi equilibrium (QE) approximations [2, 3, 4] of the full TMDD model were used to describe the disposition and interaction of a drug with a soluble target. Sampling schedules for pharmacokinetic trials featuring mAbs were evaluated, reduced with respect to the number of samples, subjects in the trials and/or trial length and optimized using PopED [5]. Expected parameter imprecision was evaluated and used to obtain population predictions of free target levels given each design. The reduced designs were compared to the original designs with respect to efficiency, parameter uncertainty and imprecision of free target levels at certain time-points. The Ds-criterion was used in the optimization and calculation of efficiency to focus on fixed-effect parameters. Based on population predictions of free target levels the likelihood of making an erroneous conclusion regarding dose selection was calculated.

Results: Reduction of the total number of samples from 1872 to 1440 in the QE model and from 624 to 288 in the QSS model did not decrease the Ds-efficiency of the designs below 90%. Substantial reduction in information content (Ds-efficiency ≤ 60%) resulted in precision of free target predictions at 14 days of 4.49-22.21% (root-mean-squared error) over a dose range, compared with 3.31-17.77% for the original design. Designs with 69% fewer samples than the original were 33% more likely to result in an erroneous dose choice to reach target suppression. Reducing the amount of samples by 23% did not affect the dose choice at an 80% power level.

Conclusions: Rich sampling designs for mAbs may be superfluous depending on the purpose of the study. Parameter uncertainty and imprecision in prediction of target levels did not always increase for substantially reduced designs. The risk of making an erroneous dose choice for future studies was marginally increased for reduced designs.

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Oskar Clewe III-42 A bronchoalveolar lavage study design framework for characterization of the rate and extent of pulmonary distribution

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Objectives: Bronchoalveolar lavage (BAL) is a semi-invasive method that enables sampling and quantification of drug concentrations from epithelial lining fluid (ELF) and alveolar cells (AC). Information about lung pharmacokinetic (PK) distribution is important in diseases such as tuberculosis where the site of action is primarily in the pulmonary tract and where plasma PK may not be a good marker when obtaining pharmacokinetic/pharmacodynamic relationships. Due to the semi-invasive nature of the BAL technique, repeated sampling within a narrow time frame from the same subject is difficult [1,2]. This poses a problem, as a characterization of the whole distribution profile then requires a large study population. This becomes even more difficult for a novel compound where the distribution characteristics might be unknown. The aim of this work was thus to develop and assess a general study design framework aimed at BAL studies in order to quantify the rate and extent of drug distribution to the pulmonary tract for a new compound using a limited number of samples.

Methods: A general PK distribution model [3], developed using rifampicin as an example was used in this work. In the model, the distribution from plasma to ELF is characterized by the extent ($R_{plasma/ELF}$) and rate (k_{ELF}) of distribution, driven by a plasma PK model. Two hypothetical drugs, one with instant and the second with slow distribution from plasma to ELF along with different number of BAL samples per subject were evaluated with only known plasma PK profile and limit of quantification (LOQ) in plasma and ELF. The evaluation was carried out using the stochastic simulation and estimation (SSE) tool provided in the Perl speaks NONMEM (PsN) [4] software.

Results: The best study BAL design for a drug with unknown lung distribution PK, is to obtain one very early and one late BAL sampling time point. The exact time points are chosen given the plasma PK profile and LOQ in plasma and ELF. Both single sample approach as well as two samples/subject designs are adequate although the latter provides less bias and lower imprecision in parameter estimates.

Conclusions: The developed study design framework is drug unspecific and enables characterization of both the rate and the extent of drug distribution from plasma to ELF. The framework includes as little as one or two samples per subject and relies only on prior information about the plasma PK profile and LOQ in ELF and plasma.

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Teresa Collins III-44 Performance of composite and serial study designs for estimation of toxicokinetic parameters.

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Objectives: In rodent studies, microsampling offers opportunity to sample main study animals for toxicokinetic (TK) assessment rather than satellite animals. This work compares various potential microsampling regimes proposed for main study animal sampling to explore which had the lowest bias and the influence of greater inter-animal variability on outcome of the TK parameter estimation was assessed.

Methods: Concentration data from a single compound, single dose, from 3 animals serially bled over 6 time-points was used as a basis for simulations (oral 1 compartment PK model). Several sampling designs were simulated including composite, serial approaches [1] and richly sampled, the latter was assumed to be true value for bias calculations for the other designs. Inter-animal variability on parameter estimates was varied by 10%, 30% and 50%. Using stochastic simulation and estimation, 1000 sample studies were simulated for each design using parameters estimated from a measured TK satellite group.

Results: Overall the sampling designs performed similarly under low inter-individual variability in terms of bias on PK parameter estimates (clearance, volume, Cmax, AUC). With increased inter-animal variability performance declined for all designs.

Conclusions: Rather than using a satellite group, we show that a reasonable TK assessment can be estimated by using microsampling within main study animals, and may provide greater insight in the development of exposure-response relationships. Additionally this work provides a 3Rs (reduction, refinement, replacement) benefit through the use of simulations as a replacement for an investigative study as well as reducing the need for satellite groups in future toxicological studies.

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Thomas Dorlo III-55 Sample size estimates for a clinical trial evaluating allometric dosing of miltefosine in children with visceral leishmaniasis in East Africa

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Objectives: We have previously shown that children treated with miltefosine for the neglected tropical parasitic disease visceral leishmaniasis (VL) are underexposed [1,2]. We therefore developed an allometric dosing regimen for children resulting in a similar drug exposure in children as adults [3]. A new exploratory pediatric clinical trial in East African VL patients is being designed to evaluate and validate this new dosing algorithm. This work aimed to provide estimates of a minimal sample size with sufficient power to evaluate clinically relevant PK parameters of the proposed allometric dosing algorithm for miltefosine in pediatric patients with VL in East Africa.

Methods: Anthropometric data from East-African VL patients were obtained from a previous clinical trial; total n=956 of whom n=454 pediatric (2-12 years). Miltefosine PK data for the targeted age group (2-12 years) were not available and concentration-time curves for the allometric dosing regimen (28 days) were therefore simulated using a well-established 2-compartment population PK model [1,3,4] and NONMEM 7.2. Secondary PK parameters (e.g. AUC, Time>EC_{50}, Time>EC_{90}) were derived. The Monte Carlo confidence interval approach was used to evaluate achieved power for various sample sizes [5]. Clinical trials (n=1000) were simulated with a random sample of patients (n=10, 15, 20,etc.) drawn from the anthropometric database available. The power to estimate the confidence intervals (95%CI) of the mean secondary PK parameters within precision intervals (15% or 20% precision) of the population mean was assessed.

Results: For AUC, the sample size minimally required to estimate the 95%CI within a 15% precision level (85%-118%) with a power of 0.95 was 25. For Time>EC_{50} and similar assumptions this was also 25. For Time>EC_{90} the sample size required to estimate 95%CI within a 20% precision level (power of 0.95) was >50. With a sample size of 25 the power to estimate the Time>EC_{90} 95%CI within 20% precision level was 0.53.

Conclusions: Application of the Monte Carlo confidence interval approach yielded rational and pragmatic estimates of required sample sizes to assess miltefosine pediatric drug exposure for a novel dosing algorithm and enabled optimization of a planned pediatric population PK trial of miltefosine for VL in East Africa.

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Eric Strömberg IV-20 Design evaluation using a bootstrapped Monte Carlo variance-covariance matrix.

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Objectives: When evaluating study designs, methods based on Monte Carlo simulations such as Stochastic Simulation and Estimation (SSE) are considered the gold standard. The parameter vectors estimated in the SSEs can be utilized to calculate an empirical variance-covariance matrix (empCOV), which may be used for design evaluation in a similar manner to the FIM, by i.e. calculating a D-criterion. However, the true empCOV-matrix can only be achieved when the number of simulations goes towards infinity. In this work this uncertainty in the empCOV and empirical D-criterion calculation is addressed by a bootstrap of the empirical D-Criteria from empCOV matrices based on samples from the estimated parameter vectors.

Methods: For two example models (one PK and one PD) the optimal designs using the FO and FOCE approximated full and block-diagonal FIMs were determined using PopED [1-2]. A completely random design was also generated for comparison with the optimal designs. In the SSE studies, 3000 simulated datasets where used to generate 3000 parameter vectors estimated (FOCEI) with NONMEM 7.2 [3] in PsN [4]. The median and the 5^{th} and 95^{th} percentiles of the D-criteria from the empCOV where calculated in MATLAB 7.13 using a 1000 iteration case-resampling bootstrap of the 3000 estimated parameter vectors where the empCOV was calculated from 3000 parameter vectors.

Results: The medians of the D-criterions of the optimal designs for the PK example ranged between 1704 and 1774 and the medians for the PD example where between 739 and 762. The average sizes of the confidence intervals were 56 and 42 for the PK and PD examples respectively. The calculated D-criteria without bootstraps were for all designs close to the medians of the confidence intervals**.**

Conclusions: In our examples**,** when calculating the empCOVs and D-criteria from the SSE parameter vectors without performing bootstraps, the results indicate that there is a difference in performance amongst all the designs. However, the confidence intervals of the D-criteria generated by the bootstraps shows that there is no significant difference between the optimal designs. Using a D-criterion from SSE parameter vectors to compare designs may include a risk of false conclusions of design superiority caused by the uncertainty of the empCOV calculation. Performing this bootstrap of empCOV matrices from the parameter vectors and instead comparing confidence intervals of D-criterion reduces the risk of false conclusions.

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Sebastian Wicha IV-47 Adaptive optimal design for the concentration tiers in time-kill curve experiments.

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Objectives: In time-kill curve (TKC) modelling, precise estimation of PD parameters is crucial, e.g. to perform reliable simulations. Conventional designs (CD) for choosing drug concentrations to be evaluated in TKC studies are usually based on multiples of the minimal inhibitory concentration (MIC) in two-fold increments. The objective of the present study was to assess the performance of such a CD by a simulation-based study using a common TKC model [1], and to compare it with a design using D-optimal concentration tiers (OD). Further, we intended to propose an adaptive optimal design (aOD) algorithm as a potential link to experimental practice.

Methods: Modelling and simulations were performed in 'R'[2]. 500 parameter sets of the TKC model were randomly sampled. Time points were 0, 2, 4, 8 and 24 h in all designs. The CD included 9 antibiotic concentration tiers of 0-16x MIC. In the ODs, 0x and 16x MIC was fixed whilst the other 7 concentration tiers were D-optimal. For the aODs, in the first stage, a reduced CD (0, 0.5, 1, 2 and 16x MIC) was used. Upon the estimates of the reduced CD, two D-optimal concentration tiers were added to the reduced CD to obtain the aOD. Based on 500 simulations each, distributions of relative error (RE; 2.5^{th}-97.5^{th} percentile) for bias and relative standard error (RSE; 95^{th} percentile) for precision were used to compare the designs.

Results: All designs allowed for precise estimation of the bacterium-specific parameters of the TKC model. For flat concentration-effect relationships (Hill factor; $H \leq 4$), the drug-specific parameters (EC50 and H) were accurately and precisely estimated for both CD and OD (RE [-13.8%; 18.3%], RSE $\leq$ 12.3%). For steep concentration-effect relationships ($4 < H \leq 10$), the ODs were superior to the CD (CD: RE [-35.1%; 74.3%], RSE $\leq$ 133% vs. OD: RE [-12.9%; 16.7%], RSE $\leq$ 10.8%). An OD with a minimal number of concentration tiers is currently assessed. The aODs performed comparably to the CD for $H \leq 4$ (aODs: RE [-14.2%; 16.4%] , RSE $\leq$ 12.7%) and also superior for $4 > H \geq 10$ (aCDs: RE [-22.0%; 31.2%], RSE $\leq$ 17.8%) by requiring only 7 instead of 9 concentration tiers.

Conclusion: For antibiotics with a considerably steep concentration-effect relationship, individual adaption of the concentration tiers in TKC studies by optimal design techniques might be beneficial for accuracy and precision of PD parameter estimates. Further research is necessary to confirm this *in silico* approach in experimental settings.

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Shuying Yang IV-50 Probability of Success with Exposure Response Modelling and Clinical Trial Simulation as a Tool to Support Decision Making

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Objectives: The aims of this work are: 1) to describe the method of evaluating probability of success by applying exposure response modelling and simulation approach; 2) to investigate the impact of model uncertainty and sample size on the probability of success.

Methods: A model-based exposure-response (ER) relationship was derived post hoc from a Phase IIb study, to describe the relationship between COPD exacerbation rate and the steady state trough drug exposure. Several forms of relationship including linear, log linear and Emax models were applied. The final model was determined using Akaike information criterion (AIC). Clinical trial simulation (CTS) was conducted to assess the probability of success of a new trial in Phase III under various scenarios. The success of a trial was defined as mean ratio of exacerbation rate

Results: A negative binomial linear model best described the relationship between COPD exacerbation rate and steady state trough drug exposure. With every unit (1 ng/mL) increase in exposure, there was about 3% (95%CI: 0.5-4.7%) reduction in the mean exacerbation rate. CTS results showed that the POS was related to dose and sample size in a nonlinear manner. The uncertainty in model selection and model parameter estimate significantly impacted the POS. Although the POS was increased with an increase in the sample size, the magnitude of increase was small. For example, at the highest dose (15mg), for a particular scenario, the POS increased from 60% to 79% as the sample size increased from 70 to 150 per arm.

Conclusions: POS can be an effective tool at each stage of drug development to support risk-benefit decision making as shown in this example. This approach integrates the various components of study design including dose, sample size, historical data and model uncertainties, and allows balanced review of impact of each component.

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