Tuesday 7 June

14:00-18:00 **Registration at the Conference Venue**

19:30-21:00 **Welcome reception**

Wednesday 8 June

08:00-08:45 **Registration**

08:45-09:00 **Welcome and Introduction**

09:00-10:20 **Immune response to drug treatment and immunotherapy** — *Chair: Oscar Della Pasqua, Dinesh De Alwis*

09:00-09:40	*Nigel Klein*	A biological perspective on immune response to drug treatment (intended and unintended effects)
09:40-10:00	*Hans Peter Grimm*	Intricate PK and PD for the novel immunocytokine CEA-IL2v and their pre-clinical to clinical translation
10:00-10:20	*Kirill Peskov*	Investigation of anti-CTLA-4 immuno-oncology therapy through a quantitative systems pharmacology model

10:20-11:40 **Coffee break, Poster and Software session I**

Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter

11:40-12:20 **Systems pharmacology** — *Chair: Charlotte Kloft*

11:40-12:00	*Kapil Gadkar*	A Six-Stage Workflow for Robust Application of Systems Pharmacology
12:00-12:20	*Rob van Wijk*	The zebrafish as model for translational systems pharmacology: expanding the allometric scale in vertebrates with five orders of magnitude

12:20-13:50 **Lunch**

13:50-15:05 **Growth (I)** — *Chair: Leon Aarons, Shasha Jumbe*

13:50-14:05	*Shasha Jumbe*	Introduction to the Gates' Healthy Birth, Growth & Development knowledge integration project
14:05-14:45	*Louise Ryan*	Trajectory modelling based on early childhood longitudinal growth data

14:45-15:05	*Niclas Jonsson*	Determinants for physical growth patterns in low- and middle-income countries
15:05-15:10	**Announcement of WCoP 2016**	*Nick Holford*
15:10-16:40	**Tea break, Poster and Software session II**	
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter	
16:40-17:20	**Growth (II)**	*Chair: Leon Aarons, Shasha Jumbe*
16:40-17:00	*Mélanie Wilbaux*	Characterizing and Forecasting Individual Weight Changes in Term Neonates
17:00-17:20	*Nick Holford*	Growth and decline of body size and composition – Prediction of the transition from pre-diabetes to Type 2 diabetes in humans
17:20-18:20	**Other applications**	*Chair: Leon Aarons, Shasha Jumbe*
17:20-17:40	*Piotr Juszczak*	Prediction of an acute kidney injury after a cardio-pulmonary bypass using a multivariate-longitudinal nonlinear mixed effect model of biomarkers concentration in blood and urine
17:40-18:00	*Thi Huyen Tram Nguyen*	The paradox of highly effective sofosbuvir combo therapy despite slow viral decline
18:00-18:20	*Rik Schoemaker*	Extrapolation of a Brivaracetam Exposure-Response Model from Adults to Children
18:30-18:50	**Special surprise...**	

Thursday 9 June

08:45-10:05	**Lewis Sheiner Student Session**	*Chair: Marylore Chenel, Aris Dokoumetzidis, Leonid Gibiansky*
08:45-09:10	*Elin Svensson*	Bedaquiline's exposure-response relationship revealed through modeling of mycobacterial load
09:10-09:35	*Solène Desmée*	Joint modelling for nonlinear longitudinal PSA kinetics and survival data in metastatic prostate cancer patients
09:35-10:00	*Stein Schalkwijk*	A physiologically-based population pharmacokinetic analysis to assess a lower efavirenz dose of 400 mg once daily in HIV-infected pregnant women
10.00-10.05	**Presentation of Lewis Sheiner student session awards**	
10:05-11:30	**Coffee break, Poster and Software session III**	

Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter

11:30-12:30	**Oncology**		*Chair: Ana Ruiz*
11:30-11:50	*Matts Kågedal*	Time-to-Event Modeling of Peripheral Neuropathy – Platform Mega-Analysis of Eight vc-MMAE Antibody-Drug Conjugates (ADCs)	
11:50-12:10	*Lucy Hutchinson*	Mathematical modelling of transient tumour growth dynamics following anti-angiogenic therapy	
12:10-12:30	*Maria Luisa Sardu*	Modelling of classified individual tumor lesions in metastatic colorectal cancer (mCRC) patients using delay differential equations	
12:30-13:50	**Lunch**		
13:50-14:35	**Tutorial: Estimation methods**		*Chair: France Mentré*
13:50-14:35	*Robert Bauer*	An overview of Estimation-Maximization Algorithms Used in Population Analysis Methods	
14:35-14:40	**Announcement of ACoP7**		*Brian Corrigan*
14:40-16:00	**Tea break, Poster and Software session IV**		
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter		
16:00-17:20	**Stuart Beal Methodology Session**		*Chair: Paolo Magni*
16:00-16:20	*Yevgen Ryeznik*	Adaptive dose finding for time-to-event outcomes with adaptive choice of patient number based on response rate	
16:20-16:40	*Sebastian Wicha*	A general pharmacodynamic interaction model based on the Bliss Independence criterion	
16:40-17:00	*Martin Fink*	Improving priors for human mAb linear PK parameters by using half-lives from pre-clinical studies	
17:00-17:20	*David McDougall*	The Impact of Model Selection for Personalised Dosing	
20:00-01:00	**Social event: Buses depart from the Conference Venue at 19:30**		

Friday 10 June

09:00-10:00	**Model-based approaches to aid in choice of dose and study design**		*Chair: Justin Wilkins*
09:00-09:20	*Lutz Harnisch*	Modelling and simulation of neurological endpoints (modified Rankin Scale [mRS] and National Institute of Health Stroke Scale [NIHSS]) to aid clinical trial design in intracerebral hemorrhage (ICH)	
09:20-09:40	*Oliver Sander*	Model-based development of the secukinumab dosing regimen for the treatment of moderate-to-severe chronic plaque psoriasis	
09:40-10:00	*Rasmus Vestergaard Juul*	Repeated time to event modelling of opioid consumption in postoperative pain	
10:00-10:20	*Thu Thuy Nguyen*	Limited sampling strategy for a population pharmacokinetic modelling of cocktail of phenotyping drugs	
10.20-10.30	**Preview of PAGE 2017**		
10:30-11:00	**Coffee break and Software session**		
11:00-12:00	**Central Nervous System Diseases**		*Chair: Nick Holford*
11:00-11:20	*Sylvie Retout*	How disease modeling and model-based meta-analyses contributed to understanding the path forward after dose discontinuation of a Phase III study in Alzheimer's disease	
11:20-11:40	*Marc Vandemeulebroecke*	A longitudinal Item Response Theory model to characterize cognition over time in elderly subjects	
11:40-12:00	*Simon Buatois*	Utilizing the items from the MDS-UPDRS score to increase drug effect detection power in de novo idiopathic Parkinson's disease	
12.00-12.10	**Closing remarks**		
12:10-12:30	**Audience input for potential PAGE2017 topics**		

PAGE2016 Abstracts

B-03: *Nigel Klein* A biological perspective on immune response to drug treatment (intended and unintended effects)

NJ Klein
UCL Institute of Child Health and Great Ormond Street Hospital NHS Trust

Objectives: 1) To present a basic overview of what the immune system is and how it works. 2) To use biological examples to highlight the intended and unintended consequences of drug treatment on the immune system

Overview/Description of presentation: The immune system is very complex and our knowledge of how it works is increasing rapidly. This has coincided with major developments in therapeutics, with an increasing array of immune modulators available for the treatment of wide range of biological conditions. This talk will describe in simple terms what the immune system is and how it works and then use a number of examples of how our attempts to manipulate the immune system have been both successful but also detrimental. Both positive and negative effects of immune modulation are not always predictable, but contribute to a greater understanding of the immune system and to future therapeutic developments. The impact of immune responses to therapies not given to modulate immunity will also be discussed. The talk will focus on examples in patients with HIV, Inflammatory Diseases such as Arthritis, Sepsis, Cancer and Stem Cell Transplants.

Conclusions/Take home message: The aim of this talk is to highlight how drugs, not necessarily directed at the immune system, can still involve the immune system. The combination of new therapeutic agents and advances in immunology is having a major influence on our approach to treating patients.

B-04: *Hans Peter Grimm* Intricate PK and PD for the novel immunocytokine CEA-IL2v and their pre-clinical to clinical translation

Hans Peter Grimm (1), Flavio Crameri (1), Heather Hinton (2), Dietrich Türck (1), Hanna Silber (1), Benjamin Ribba (1)
Roche Pharmaceutical Research and Early Development, (1) Roche Innovation Center Basel and (2) Roche Innovation Center Zurich

Objectives: To support entry into human and Phase I design of the tumor targeted immunocytokine CEA-IL2v by leveraging non-clinical multi-scale data using mixed effects PK and PKPD modeling.

Methods: PK and PD data from single and multiple dose studies in a total of 40 non-human primates with roughly 12 PK and PD observations per subject were pooled. PK was modeled using several evolving versions of target-mediated disposition in which the IL-2 receptor is the major driver of the clearance of CEA-IL2v. A complicating factor is that the IL-2 receptor is up-regulated by the pharmacological action of CEA-IL2v itself. In a second step, a number of PD measures (including activation markers and cell numbers of several lymphocyte sub-sets) were analyzed to characterize the potency of CEA-IL2v on each of these. All PK and PD analyses were performed using MONOLIX. Model based projection of human exposure was performed mainly based on allometric principles and were incorporated in the design of the First In Human (FIH) study. The preclinical modeling work was applied as a starting point for the analysis of clinical data.

Results: The PK of CEA-IL2v was found to be strongly governed by the IL-2 receptor which in its turn is induced by the pharmacological action of CEA-IL2v itself. This feed-back pattern explains the intricate PK of CEA-IL2v. PD is observed at multiple time scales ranging from a minutes (phosphorylation of STAT5) to hours (up-regulation of CD25 and CD69 on lymphocytes) to days (expansion of cell populations). The PD behavior was captured by turnover models, however complicated by the trafficking of cells between tissues and blood. The relative potency on the various lymphocyte populations was found to be in line with the desired profile for cancer immunotherapy. The projection of human PK and PD, despite some over-prediction of exposures at low doses, allowed a safe and efficient FIH study design.

Conclusions: We have shown how thorough analysis of non-clinical PK and PD data supported the pre-clinical to clinical translation by: 1. providing explanations to complex PK behavior, 2. confirming the relative potency on lymphocyte subpopulations, 3. guiding dose selection and scheduling of the assessments in the FIH study, and finally 4. in prototyping PK and PKPD models that are now employed with human data.

B-05: *Kirill Peskov* Investigation of anti-CTLA-4 immuno-oncology therapy through a quantitative systems pharmacology model

Yuri Kosinsky(1), Kirill Peskov(1), Boris Shulgin(1), Oleg Stepanov(1), Veronika Voronova(1), Eric Masson(2), Gabriel Helmlinger(2)
(1)M&S Decisions LLC, (2)Quantitative Clinical Pharmacology, Early Clinical Development, AstraZeneca

Objectives: Immune cell pathways and their corresponding drug targets are the object of intense preclinical and clinical research. Complex kinetics, multiplicity of therapeutic targets, and potential for synergistic drug combinations all make the use of a quantitative systems pharmacology model (QSP) a necessity. An conceptual picture of immune responses to tumor cell progression and treatment has been described, based on a basic understanding of the immuno-oncology (IO) players and processes [1]. A quantitative QSP model was developed, focusing on dynamic interactions between key immune cell types and cancer cells, soluble mediators, and IO checkpoint inhibitors within the tumor microenvironment. The main objective of this study was to properly incorporate and qualify, within the QSP model, the pleiotropic effects observed following CTLA-4 blockade mechanism.

Methods: The QSP model is represented by a system of ordinary differential equations. The core model was built and initially qualified based on *in vivo* mouse data published in multiple literature sources. Model parameters were calibrated based on levels of selected cytokines, immune cell counts in tumor and plasma, and tumour dynamics data (growth & shrinkage under experimental treatment). Model incorporation of anti-CTLA-4 treatment modulated mechanisms was performed based on preclinical studies from the literature as well [2,3].

Results: Several possible mechanisms linking CTLA-4 blockade to tumor growth inhibition effects were evaluated using outcomes from the QSP model. As a result, we identified the following mechanistic links, which are minimally necessary in order to correctly describe all published *in vivo* data on anti-CTLA-4 treatment: (1) increase in proliferation of CTLs and regulatory T lymphocytes (Tregs); (2) inhibition of the immuno-suppressive mechanism between Tregs and CTLs, which is most likely caused by the depletion of CTLA-4/CD80 interactions. Additionally, with these minimally necessary relations incorporated, a model-based sensitivity analysis was performed. It revealed a key set of parameters which may drive inter-animal variability in treatment outcome (tumor growth inhibition).

Conclusion: We developed an QSP model, which adequately describes regulatory dynamics of the IO multi-cell cycle, in experimental mouse models and in response to various anti-CTLA-4 inhibition therapies. Model-based simulations revealed key elements of CTLA-4-related regulatory mechanisms which affect tumor growth inhibition and parameters responsible for the observed inter-individual variability.

References:
[1] Chen DS and Mellman I. Oncology Meets Immunology: The Cancer-Immunity. Immunity, 2013, 39, 1-10.
[2] Peggs, K. S., et al. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti–CTLA-4 antibodies. J Exp Med, 2009, 206: 1717-25.
[3] Selby et al. Anti-CTLA-4 Antibodies of IgG2a Isotype Enhance Antitumor Activity through Reduction of Intratumoral Regulatory T Cells. Cancer Immunol Res. 2013, 1:32-42

B-07: *Kapil Gadkar* A Six-Stage Workflow for Robust Application of Systems Pharmacology

Kapil Gadkar, Dan Kiroauc, Don Mager, Piet van der Graaf, Saroja Ramanujan
Genentech, University at Buffalo, Leiden University

Objectives: The area of Quantitative Systems Pharmacology (QSP) is seeing increasing adoption and efforts in pharmaceutical research and industry settings. QSP however represents a different approach than more traditional pharmacometrics modeling and simulation, and thus, involves different technical considerations. QSP models are typically less driven by fitting of individual datasets but involve integration of diverse datasets to enable the mathematical representation of the biology of interest. Along with an expanded scope due to broader intended applications, this can potentially lead to under-constrained models. Further, QSP models are often used for testing biological/clinical hypotheses and for predictions in scenarios or patient populations where clinical data is limited, These novel aspects of QSP necessitate different technical workflows and approaches.

Methods & Results: Here we present a robust workflow that, in its entirety or in sections, has been successfully applied in QSP-based efforts to address many of the novel challenges these efforts face. This workflow involves: (1) initial data evaluation and scope specification; (2) model structure identification and implementation; (3) initial calibration & validation of "reference" virtual subjects and (4) of alternate virtual subjects and virtual "populations"; (5) model-based prediction; and (6) iteration with laboratory and clinical data acquisition. Technical approaches for each of these stages are discussed, including: aggregation of diverse data; selection of modeling formalism; development and identifiability of model structure(s); parameter optimization, sensitivity, and uncertainty/variability; resulting robustness of associated predictions; and experimental design guidance. In this context, we also review published systems modeling efforts that illustrate this workflow and the technical approaches discussed.

Conclusions: We have presented a staged workflow for the application of QSP. Notably, this workflow helps address several questions and criticisms commonly facing QSP projects. By providing a common, organized strategy along with guidance on technical approaches to address these and other considerations, we believe this workflow and subsequent evolution thereof can offer a useful framework for the execution, communication, and acceptance of QSP endeavors.

B-08: *Rob van Wijk* The zebrafish as model for translational systems pharmacology: expanding the allometric scale in vertebrates with five orders of magnitude

R.C. van Wijk[1], E.H.J. Krekels[1], V. Kantae[2], A.C. Harms[2], Y. Guo[3], W.J. Veneman[4], F.J. Verbeek[3], T. Hankemeier[2], H.P. Spaink[4], and P.H. van der Graaf[1]
Systems Pharmacology Cluster, [1] Division of Pharmacology & [2] Division of Analytical Biosciences, Leiden Academic Centre for Drug Research (LACDR), Leiden University, The Netherlands [3] Imaging and BioInformatics Section, Leiden Institute of Advanced Computer Science (LIACS), Leiden University, The Netherlands [4] Division of Animal Sciences and Health, Institute of Biology Leiden (IBL), Leiden University, The Netherlands

Objectives: The objective was to develop a method to quantify pharmacokinetics (PK) in zebrafish larvae. This can improve the increasingly used screens in zebrafish larvae, which ignore influence of PK on observed effects[1-3]. Indeed, systemic exposure is required to interpret the observed effects and derive a concentration-effect relationship. Additionally, estimated PK parameters could be used for interspecies scaling and optimization of preclinical experiments. To reach our objective, three aspects were essential: 1) accurate quantification of drug amounts in extreme small samples, 2) mixed effects PK modelling, and 3) determination of the exact volume of zebrafish larvae.

Methods: Zebrafish larvae were exposed to 1 mM paracetamol at 3 days post fertilization (dpf) for 10-300 minutes. At different time points, 3 replicates of samples with 5 larvae were lysed and paracetamol amounts were quantified by UPLC – Quadrupole TOF MS. A one and two compartment model with zero order absorption and first order elimination were tested in NONMEM 7.3. Total volume of distribution was fixed to one, yielding a relative clearance estimate. The volume of a single zebrafish was determined using VAST microscopy and silhouette 3D modelling. This volume was used to calculate the absolute clearance and bodyweight of the zebrafish larvae. The absolute clearance was compared to literature values of higher vertebrates in a log-log plot of clearance versus bodyweight.

Results: In all samples, absolute paracetamol amounts could be accurately quantified. A one compartment model with proportional error model for residual variability best described the data. Relative clearance was estimated at 1.7% of larva volume/min. Residual variability was 9.73%. The volume of a single zebrafish larva at 3 dpf was estimated to be 260 nL yielding a weight of 286 ug, being five orders of magnitude lighter than the mouse. Absolute clearance was 265.2 nL/h, which correlates well with the relationship between clearance and bodyweight in higher vertebrates.

Conclusions: We successfully developed a method to quantify drug PK in zebrafish larvae, a promising model system which has the potential to improve the understanding of drug pharmacology in early drug development and replace animal testing. This method will be further developed to include metabolic clearance, with the objective to estimate (active) metabolite exposure, as well as the possibility of interspecies scaling of different elimination pathways.

References

[1] A.J. Rennekamp, R.T. Peterson, Current Opinion in Chemical Biology 24: 58-70 (2015)
[2] S. Berghmans et al, Journal of Pharmacological and Toxicological Methods 58:59–68 (2008)
[3] P. Goldsmith, Current Opinion in Pharmacology 4: 504-512 (2004)

B-10: *Shasha Jumbe* Introduction to the Gates' Healthy Birth, Growth & Development knowledge integration project

Shasha Jumbe
Bill & Melinda Gates Foundatiom

B-11: *Louise Ryan* Trajectory modelling based on early childhood longitudinal growth data

Louise Ryan (1), Craig Anderson (1), Stef Van Buuren (2) and various members of the HBGDki Team
(1) University of Technology Sydney, and Australian Research Council Centre of Excellence in Mathematical and Statistical Frontiers; (2) Netherlands Organization for Applied Scientific Research, Leiden, the Netherlands

Objectives: Understand the pros and cons of various approaches to longitudinal growth modelling. Understand how various measures reflecting different growth patterns can be extracted from these models and used to predict other outcomes of interest.

Overview/Description of presentation: We will describe a unique database gathered through the efforts of the Bill and Melinda Gates Foundation that includes twenty nine longitudinal studies of child growth and development. The studies range in size from 197 children, to over 1 million children, with the median number of 764 children per study. The studies varied considerably in terms of the number of repeated measurements per child, with the smallest being an average of 6 measurements per child and the median being an average of 13 measurements per child. Available growth measurements include child weight as well as length or height, depending on the child's age.

While one could work directly with these measurements, we chose to model age and gender adjusted Z-scores for height (HAZ) and weight WAZ), computed relative to the WHO child growth standards (see http://www.who.int/childgrowth/standards/en). The advantage of working with HAZ and WAZ rather than raw height and weight values is that models do not need to account for gender and age.

After presenting various modelling options, including random effects models based on splines and functional data analysis methods, we will assess how well the various models do in capturing the patterns represented in the studies. We assess model fit through mean square error computed by comparing observed and predicted values for a hold-out sample. We show that a linear spline model (the so called broken stick model) and a recently developed functional data analysis approach [1] do best overall. Application of the broken stick methodology requires specification of the number and location of knots. We present some sensitivity analysis that explores the impact of varying the number and location of knots, finding that in our setting, the method is relatively robust. Surprisingly, the broken stick model consistently outperforms a penalized spline approach which has a tendency to over-smooth the data. The broken stick model has some computational advantage relative to the functional data analysis method, with the latter being slower to fit in general and sometimes encountering issues with convergence. This particular implementation of functional data analysis is designed to work in sparse data settings where observations are available at only a relatively small number of time points.

We discuss how child growth trajectories can be represented by derivatives computed from the fitted models. We show that numerical derivatives do just as well as analytical derivatives in capturing changing curve shapes. However, we do find that the estimated derivative is quite sensitive to the curve fitting method that was used. We show how estimated derivatives relate to classical measures of child growth, including growth velocity and conditional Standard Deviation Scores (SDS), both of which have been widely advocated in the child growth literature [2]. We illustrate how these measures can be used as predictors for subsequent outcomes of interest, for example, cognition. We conclude by discussing some of the

challenges faced when analysing complex longitudinal growth data and outline areas where further research and exploration would be useful.

Conclusions/Take home message: Child growth data can be well captured using a linear spline model that includes random effects to allow individual childrens' departures from overall population curves. More sophisticated methods based on functional data analysis methodologies also do very well, but are computationally more challenging.

References:

[1] Xiao, L., Ruppert, D., Zipunnikov, V., and Crainiceanu, C. (2014+), Fast covariance estimation for high dimensional functional data, Statistics and Computing, to appear.
[2] Cole, TJ (1995). Conditional reference charts to assess weight gain in British infants. Archives of Disease in Childhood 73: 8-16.

B-12: *Niclas Jonsson* Determinants for physical growth patterns in low- and middle-income countries

E. Niclas Jonsson (1), Joakim Nyberg (1), Jonas Häggström (2), Lifecycle Auxology & Neurocognitive Development team (3), representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community.
(1) Pharmetheus AB, Uppsala, Sweden, (2) HDC, Stockholm Sweden, (3)

Objectives: The objective of growth monitoring in children is early detection of growth failure, to allow timely remedial interventions and prevention of further growth failure. Our goal was to identify predictors for physical growth between 0-15 years of age in low and middle-income countries.

Methods: Data from low- and middle-income countries (LMIC) was used to build a longitudinal non-linear mixed effects model for height-for-age Z-scores (HAZ) (heights which are age normalized to WHO standard heights) between 0 to 15 years of age. Approximately 82000 observations from 15000 subjects spread across five different countries were used in the analysis.

An inverse Bateman model was used to describe the general trend of initially declining HAZ scores followed by a longer-term recovery phase. Between site differences and between individual differences were accounted for by site specific and individual specific random effects, respectively. The influence of the 26 covariates on the four model parameters was investigated using a modified SCM [1] search algorithm supported by PsN [2]. The relevance of the covariates in the final model was quantified in terms of their impact on phenotypic features of the predicted age-HAZ responses, for example maximum attained growth failure, ie., minimum HAZ (nadir), time of nadir and rate of growth recovery.

Results: The HAZ score at birth for a typical child across all sites was estimated to be -0.13. The half-life of decline to the nadir of -2.5 was estimated to 0.6 years. The half-life of recovery from nadir to a HAZ score of -0.9 at age 15 was estimated to be 8.5 years.

The final model included 14 parameter-covariate relationships and the covariates with the largest impact on the predicted growth curves were birth weight, length of maternal education and maternal height. For example, the predicted nadir for a child to a tall mother (163 cm) compared a child to a short mother (146 cm) was 26% smaller, while the corresponding recovery rate was 61% shorter. Other covariates in the final model included degree healthcare utilization, type of toilet and maternal empowerment.

Conclusions: The model successfully described the growth trajectories across the five sites. The identified covariates can be used to better understand the determinants for physical growth development in low- and middle-income countries, and the model can be used to support the design of future studies.

Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative

References:
[1] Automated covariate model building within NONMEM. Jonsson EN, Karlsson MO. Pharm Res. 1998 Sep;15(9):1463-8.
[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.

B-13: *Nick Holford* Announcement of WCoP 2016

Nick Holford
WCoP organising committee

B-15: *Mélanie Wilbaux* Characterizing and Forecasting Individual Weight Changes in Term Neonates

Mélanie Wilbaux (1), Severin Kasser (2), Sven Wellmann (2), Olav Lapaire (3), Johannes N. Van Den Anker (1, 4), Marc Pfister (1, 5)

(1) Division of Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel (UKBB), Basel, Switzerland, (2) Division of Neonatology, University of Basel Children's Hospital (UKBB), Basel, Switzerland, (3) Division of Obstetrics and Gynecology, University Hospital Basel, Basel, Switzerland, (4) Division of Pediatric Clinical Pharmacology, Children's National Health System, Washington, DC, USA, (5) Quantitative Solutions LP, Menlo Park, CA, USA.

Objectives: As part of normal physiology newborns lose body fluid during the first days of life. The magnitude of initial fluid loss and consecutive weight gain vary strongly among neonates, and excessive weight loss in some newborns can result in long-term complications. Objectives of this work were to (i) develop a semi-mechanistic model that characterizes physiological weight changes during the first week of life; (ii) identify effects of maternal and neonatal factors, and (iii) provide an online tool to forecast individual weight changes.

Methods: Longitudinal weight data and individual characteristics from 1335 healthy term neonates exclusively breastfed were available up to 1 week of life. A semi-mechanistic turnover model was developed characterizing the weight change as a function of a changing net balance between time-dependent rates of weight gain (Kin) and first-order weight loss (Kout). Different time-dependent functions were tested such as linear, exponential or saturable functions. Population analysis was implemented using NONMEM 7.3. Model selection was based on statistical criteria, goodness-of-fit plots and simulation-based diagnostics. Clinically relevant covariates testing was performed utilizing a standard stepwise forward-backward covariate model building approach. Data from 300 additional term neonates were used for advanced evaluation of developed model.

Results: Kin was modeled as an exponential function of time. Kout was modeled with a saturable function to describe initial decrease due to fluid loss followed by an exponential time-dependent increase. Males had higher birth weights (WT0) than females. Gestational age had a positive effect on WT0 and Kin, whereas mother's age had a positive effect on WT0 and a negative effect on Kin. Advanced evaluation demonstrated good predictive performance of the model (bias=0.01%, precision=0.52%). Furthermore, the model was able to accurately forecast individual weight changes up to 1 week with only 3 initial weight observations during the first 2 days (bias=-0.74%, precision=1.54%).

Conclusions: We developed the first model describing physiological weight changes in healthy term exclusively breastfed neonates during the first days of life. We provide a user-friendly online *NeoWeight Prediction* tool allowing caregivers to monitor individual weight changes, and further personalize and optimize care for neonates. This model will be expanded with data from preterm, formula-based fed and sick neonates.

B-16: *Nick Holford* Growth and decline of body size and composition – Prediction of the transition from pre-diabetes to Type 2 diabetes in humans

Nick Holford (1), Tim Kenealy (2)
(1) Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand (2) Department of General Practice, University of Auckland, New Zealand

Objectives: The most common consequence of obesity is the development of Type 2 diabetes. Body mass index (BMI) is widely used to quantify obesity but it is a size metric without a clear biological basis. Fat mass, on the other hand, is anatomically and physiologically identifiable. Increased fat has been suspected as the causal factor for developing Type 2 diabetes and decreased survival [1, 2]. The objectives of this study are:

1. to describe the time course of growth and decline of body size and composition in pre-diabetic humans.
2. to identify factors related to body size and composition predictive of the time to develop Type 2 diabetes.

Methods: A cohort of 21,002 adult pre-diabetic patients were followed in a New Zealand general practice setting. Total body weight (TBW), height (HT), sex, ethnicity and current smoking habit were recorded at each visit until a diagnosis of Type 2 diabetes was made or the study ended. Fat free mass and fat mass were predicted from weight, height and sex [3]. The clinical outcome event was the time to diagnosis of Type 2 diabetes. Mixed effect joint models of TBW, HT and time to event [4] were used for model selection and parameter estimation with NONMEM 7.3.

Results: There was a significant trend for TBW (-0.46 kg/y) and HT (-0.12 cm/y) to decrease with age. Significant covariates for baseline TBW were sex, smoking, and race and for rate of decline covariates were sex and smoking. The rate of loss of TBW was 13% faster in women and 33% faster in women smokers. Smaller effects were seen with HT. Predicted fat mass tended to increase in young adults before declining. The baseline hazard of developing Type 2 diabetes had a Gompertz distribution. Explanatory factors were sex, smoking, race and body size. The time course of fat mass was a significant predictor of the hazard.

Conclusions: We have developed a mixed effects model for growth in pre-diabetic humans. The time course of TBW and HT can predict changes in size metrics such as BMI and fat mass in this high risk population. The time to event model provides quantitative evidence for the lipotoxicity theory [2] of the pathogenesis of Type 2 diabetes. In a drug development setting these models can quantify the benefits of therapeutic goals based on weight reduction and be used to simulate more effective clinical trials [5].

References:

[1] McAuley, P.A., et al., *Fitness, fatness, and survival in adults with prediabetes.* Diabetes Care, 2014. **37**(2): p. 529-36.
[2] Sivitz, W.I., *Lipotoxicity and glucotoxicity in type 2 diabetes. Effects on development and progression.* Postgrad Med, 2001. **109**(4): p. 55-9, 63-4.
[3] Janmahasatian, S., et al., *Quantification of lean bodyweight.* Clin Pharmacokinet, 2005. **44**(10): p. 1051-65.
[4] Holford, N., *A Time to Event Tutorial for Pharmacometricians.* CPT: pharmacomet. syst. pharmacol., 2013. **2**: p. e43 doi:10.1038/psp.2013.18.

[5] Holford, N., S.C. Ma, and B.A. Ploeger, *Clinical trial simulation: a review.* Clin Pharmacol Ther, 2010. **88**(2): p. 166-82.

B-17: *Piotr Juszczak* Prediction of an acute kidney injury after a cardio-pulmonary bypass using a multivariate-longitudinal nonlinear mixed effect model of biomarkers concentration in blood and urine

Piotr Juszczak
Near Patient Testing, Novartis, Basel, Switzerland

Objectives: An acute kidney injury during a cardio-pulmonary bypass is associated with high morbidity and mortality. The current standard of care to diagnose an acute kidney injury is based on an increase creatinine concentration in blood. The increase of creatinine concentration may indicate lower renal filtration rate but not necessary kidney damage. In addition, primarily damage to only a specific part of a kidney, i.e. glomeruli, affects a creatinine filtration rate. Finally, after a kidney insult long time, on average several days is required for a creatinine to increase to a level necessary for a diagnosis of an acute kidney injury.

An objective of this work is a development of a longitudinal model, that can be use as an early diagnostic test, by comparing concentration of multiple biomarkers, associated with kidney damage, inflammation and repair pathways of patients with various severity of an acute kidney injury.

Methods: A multivariate-longitudinal-nonlinear mixed effect model was developed to model concentration of biomarkers in blood and urine, at specific time, following a cardio-pulmonary bypass, for patients that were diagnosed with various stages of an acute kidney injury. A horseshoe prior [1] was used to select the most informative subset of biomarkers that gives the best diagnostic performance within the first 6 hours window post a cardio-pulmonary bypass. Three studies with more than 600 adult patients were used to derive the model. The informative priors, of the model parameters, were derived from physiological models [2-3] and a literature review. All models were implemented in Stan 2.9.3 [4].

Results: Prediction performance of the model was measured using an external cross-validation, i.e. patients from studies that were not used during the model development stage. By comparing a patient biomarkers concentration, at any time in the first 6 hours post a kidney insult, the proposed model predicts an acute kidney injury 82 (67.9, 88.8) hours earlier than the standard of care test based on an increase of creatinine concentration in blood, for 80% of patients. The median area under a receiver operating characteristic curve is equal to 0.84 for the proposed model. For a single prediction threshold, which corresponds to 0.8 of a true positive rate, a false positive rate equals 0.23.

Conclusions: The developed model allows for prediction of an acute kidney injury on average 82 hours earlier than current standard of care for 80% of patients, however it requires measurement of concentration of multiple biomarkers in blood and urine.

References:

[1] Carvalho C., Polson N. and Scott J.; Handling sparsity via the horseshoe, JMLR W&CP 5:73-80, 2009.
[2] Mechanisms of Acute Kidney Injury and Repair, Bonventre J. 2009
[3] Mathematical Physiology II: Systems Physiology, Keener J. and Sneyd J.
[4] Stan Development Team. 2016. *The Stan Math Library*, Version 2.9.0.

B-18: *Thi Huyen Tram Nguyen* The paradox of highly effective sofosbuvir combo therapy despite slow viral decline

Thi Huyen Tram Nguyen (1), Jeremie Guedj (1), Laetitia Canini (2,3), Anu Osinusi (4), Phillip S. Pang (4), John McHutchison (4), Henry Masur (5), Anita Kohli (6), Shyam Kottilil (7) & Alan S Perelson (2)
(1) IAME, UMR 1137, INSERM, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France; (2) Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM; (3) Epidemiology Research Group, University of Edinburgh, Edinburgh, Scotland, UK; (4) Gilead Sciences, Foster City, CA; (5) Critical Care Medicine Department, NIH Clinical Center, Bethesda, MD; (6) Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc. (formerly SAIC–Frederick, Inc.), Frederick National Laboratory for Cancer Research, Frederick, MD; (7) Laboratory of Immunoregulation, NIAID, NIH, Bethesda, MD

Objectives: The Synergy trial showed that high cure rates for HCV infection could be achieved after 12-week treatment with sofosbuvir (SOF) and ledipasvir (LDV), and after only 6 weeks if GS-9669 (a non-nucleoside polymerase inhibitor) or GS-9451 (a protease inhibitor) was added [1]. Here we used viral kinetic models to better understand the effect of each drug in this very rapid and effective cure of HCV.

Methods: We conducted a pooled analysis of the early viral kinetics in patients treated with SOF+ribavirin (RBV) [2], SOF+LDV and SOF+LDV+GS9669/GS9451. Viral kinetics were fitted using a multiscale model that can distinguish the effect of blocking vRNA replication, ε_α, from blocking viral assembly/secretion, ε_s [3].

Results: The viral load decline was initially much more rapid in all arms of Synergy than in patients treated with SOF+RBV. This was attributed in our model to a high effectiveness of LDV in blocking viral assembly/secretion (ε_s=99.7%). However by day 3, patients treated with SOF+RBV achieved largely comparable levels of virus as the patients in all arms of Synergy, demonstrating a high effectiveness of SOF in blocking vRNA production (ε_α=99.96%). Surprisingly, the total effectiveness in blocking vRNA production was significantly lower in patients receiving SOF+LDV±GS-9669 (ε_α=96.5%, $P<10^{-10}$) and, to a lesser extent, SOF+RBV±GS-9451 (ε_α=98.5%, $P<10^{-10}$). Eventually, the final phase of viral decline was largely similar in all groups, and similar to that observed with IFN-based therapies, in contradiction with the large SVR rates of 95% observed. To explain this discrepancy, we hypothesized that most of the virus observed at EOT was non-infectious. Using a model that accounts for this hypothesis, we quantified the amount of infectious virus over time in dual or triple therapy, and predict the outcome of shorter treatment durations, e.g., 4 weeks. The validity of this hypothesis is being evaluated *in vitro* using in an infectious system by comparing the proportion of infectious virus over time under different treatments.

Conclusions: The kinetics of viral decline in patients of the Synergy trial was remarkably slow in regard of the very rapid cure of HCV. This suggests that HCV RNA is not a reliable marker for predicting outcome of treatment containing SOF+LDV. Additional mechanisms of action that are not reflected in the observed viral load, such as production of non-infectious virus, may explain the high cure rates.

References:
[1] Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. Lancet 2015.Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. Lancet 2015.
[2] Osinusi A, Meissner EG, Lee Y-J, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. J. Am. Med. Assoc. 2013;310:804–811.

[3] Guedj J, Dahari H, Rong L, et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. Proc. Natl. Acad. Sci. U. S. A. 2013;110:3991–3996.

B-19: *Rik Schoemaker* Extrapolation of a Brivaracetam Exposure-Response Model from Adults to Children

Rik Schoemaker(1,3), Armel Stockis(2)
(1) SGS Exprimo, (2) UCB Pharma, (3) Current affiliation: Occams

Objectives: To scale an existing adult population PK/PD model for brivaracetam (BRV) into children, using a combined adult-pediatric PK/PD model for levetiracetam (LEV), a compound with a similar primary mechanism of action, and to predict the effective dose of BRV in children aged 4 to 16 years.

Methods: A population PK/PD model has been previously developed to describe the relationship between BRV plasma concentrations and seizure frequency change from baseline in adult subjects. A pediatric population PK model is available for BRV. For LEV, both PK and PD data are available in adults and children. In order to support the extrapolation of PD in BRV to children aged ≥4 to

The model described seizure counts using a negative binomial distribution taking previous day seizure frequencies into account [1], and using a mixture model to separate a 'placebo like' and a 'responder' sub-population.

VPCs were used to ascertain the ability of the LEV adult/pediatric PK/PD model to adequately simulate trial outcome in terms of percentage change in seizure frequency from baseline, and fraction of subjects with ≥50% decrease in seizure frequency. PK and PD simulations for BRV were performed in children for a range of mg/kg doses to predict BRV effect in pediatric subjects, and aid trial design decisions.

Results: The LEV PK/PD model was able to describe both the adult and the pediatric data using the same drug effect population parameters, and using a model structure very similar to the existing adult PK/PD BRV model. VPCs illustrated that the LEV adult/pediatric PK/PD model was capable of simulating the observed trial outcomes. Simulation with the adult BRV PK/PD model in combination with the pediatric BRV population PK model, allowed characterization of the dose-response curve, suggesting maximum reponse at BRV 4 mg/kg/day dosing in children.

Conclusions: Application of a population PK/PD count model to trial data from a registered compound with a similar primary mechanism of action, allowed prediction of drug effects in pediatric patients for BRV that will help plan future studies.

References:
[1] Ahn JE, Plan EL, Karlsson MO and Miller R. Modeling Longitudinal Daily Seizure Frequency Data From Pregabalin Add-On Treatment. J Clin Pharmacol 2012 52: 880-892.

C-01: *Elin Svensson* Bedaquiline's exposure-response relationship revealed through modeling of mycobacterial load

Elin M. Svensson (1), Stefaan Rossenu (2), Mats O. Karlsson (1)
1. Dept. Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. 2.Dept. Clinical Pharmacology & Pharmacometrics, Janssen Research & Development, Beerse, Belgium

Objectives:
Pulmonary tuberculosis (TB) remains a dramatic health problem with an estimated incidence of 9.4 million cases in 2014, of which 0.5 million were caused by multi-drug resistant (MDR) TB (1). There is an acute lack of knowledge of how to best select regimens of second-line anti-TB drugs and this uncertainty is linked to poor description of dose-exposure-response relationships.

Bedaquiline (BDQ) was recently granted conditional approval for treatment of MDR-TB based on Phase II studies (2,3) and is now in use (4). The efficacy was primarily assessed on time to sputum culture conversion (TSCC, i.e. when mycobacteria can no longer be detected in sputum) and conversion status and cure rates at month 30. However, the performed analyses could not identify a relationship between BDQ exposure and any of these outcomes (2).

In this work we aimed to characterize an exposure-response relationship by modeling repeated measures of mycobacterial load (MBL), quantified by sputum cultures in a mycobacterial growth indicator tube system (MGIT). The results were discussed in relation to previously predicted (5–7) and recently confirmed drug-drug interactions (8).

Methods:
Data were obtained from a registration phase IIb study (TMC207-C208). The design was randomized, double-blind and placebo-controlled; enrolling newly diagnosed patients with pulmonary MDR-TB. All patients were treated with a background regimen of 5 second-line anti-TB drugs to which either placebo or BDQ was added. The duration of the addition was either 8 weeks (pilot) or 24 weeks (majority). BDQ was dosed at 400mg QD the first 2 weeks and thereafter 200mg 3 times per week. The study was conducted in accordance with Good Clinical Practice standards and received ethical approval from appropriate local authorities.

Triplicate sputum samples were collected at the day prior to treatment initiation, weekly until week 8 and bi-weekly until week 24. MGIT cultures were initiated from each sample and the time to positivity (TTP), i.e. a signal indicating presence of *M. tuberculosis*, was automatically recorded. TTP is a measure of MBL, with a shorter time indicating a higher bacterial burden. Samples without a signal at 42 days were classified as censored negative.

A model of MBL in patients was linked to the hazard in the time-to-event (TTE) model of TTP, and PK, interindividual variability (IIV) and covariate effects were evaluated on parameters of the MBL model. Individual secondary PK metrics were obtained from a previously developed model (9). The analysis was performed in NONMEM 7.3 with the Laplace estimation method. Parameter uncertainty was assessed with SIR (10).

Posterior predictive checks (PPC) of TSCC calculated based on observed and simulated datasets (n=100) were performed. The clinical importance of detected covariates, quantified by changes in TSCC and

proportion without SCC at week 20, was assessed through simulations including parameter uncertainty (n=100) for a large dataset (2000 subjects with a specific set of characteristics per scenario).

Results:
TTP data from 206 patients were available; only samples collected during the intervention period were considered. After curation a dataset including 6330 observations (59.8% positive) from 193 individuals collected up to week 20 were used for model building.

The developed PD model included 3 simultaneously fitted components: (i) a longitudinal representation of MBL in patients over time on treatment, (ii) a model of the probability of bacterial presence in a sputum sample and (iii) a TTE model for TTP in MGIT. The MBL was described by a mono-exponential decline over time on treatment where the number of bacteria at start was informed by each individual's observed baseline mean TTP. IIV with a Box-Cox transformed distribution was included on the half-life of the decline. The probability of bacterial presence was linked to MBL by an Emax-function including the maximal risk (P_{max}) and the MBL value corresponding to 50% of P_{max}. The hazard in the TTE model was proportional to the current number of bacteria in the growth tube. The number of bacteria in the tube over time was described by an inoculum size defined by the MBL and a logistic growth function.

The joint PD model described the TTP data well and the PPC demonstrated that also TSCC in the 2 study arms was well predicted. The model of probability of bacterial presence handled the increasing portion of negative samples, providing the characteristic shape of TTP survival curves reaching a plateau after about 25 days. Of previously described models the present model shows most similarity to (11). However, by including the probabilistic element, it was possible to use MBL inoculum size as the driver of TTP hazard without incorporating mechanistically unjustified changes in the bacterial growth processes in the MGIT system over time on treatment (11). The estimated initial doubling time in the MGIT tube was 33h (RSE 5%) which is in line with observed *in vitro* growth rates for *M. tuberculosis*.

Early BDQ exposure ($AUC_{0\text{-}24h}$ at day 14) was found to significantly affect the half-life of MBL through an Emax-function. The maximal effect could not be estimated reliably due to the limited range of observed exposures and was therefore fixed to -100%. EC_{50} was estimated to 52 µg/mL*h (RSE 36%) and fell within the observed range of exposures (10-94 µg/mL*h). Simulations of the impact showed that the proportion of patients without SCC at week 20 is expected to decrease from 28% (95%CI 23-34) in the placebo arm to 19% (15-22), 14% (10-17) or 8% (5-11) in patients with half median, median (35 µg/mL*h) or double the median BDQ exposure, respectively. In addition, patients with (pre-) extensively drug resistant TB were found to clear mycobacteria 31% (RSE 22%) slower than patients with MDR-TB, leading to 2-4 weeks later median TSCC.

Conclusions:
A novel model describing MBL in MDR-TB patients with 3 linked sub-components was developed. In contrast to simpler analyses of secondary PD metrics based on the same data, our model could detect and describe an exposure-response relationship for BDQ.

The model shows that higher BDQ levels early during treatment lead to faster response. This may have implications on coadministration of BDQ with drugs that lower exposure such as efavirenz and rifampicin (which induce BDQ CL to 207% and 478% of normal, respectively), and strengthens the earlier recommendations against concomitant use at standard BDQ dose (5,7). Furthermore, the increased exposure when coadministered with lopinavir/ritonavir (inhibiting BDQ CL to 35% of normal (6,8)) could lead to faster SCC. The link between week 2 exposure and bacteriological response may also provide an opportunity for early assessment of individual patients' chance of favorable outcome.

This characterization of BDQ's exposure-response relationship could inform optimization of novel anti-TB regimens and their application also in TB-HIV coinfected patients.

References

[1] World Health Organization. Global Tuberculosis Report 2015.
[2] Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723–32.
[3] Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2015 Dec 2.
[4] Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2015;19(8):979–85
[5] Svensson EM, Aweeka F, Park J-G, Marzan F, Dooley KE, Karlsson MO. Model-Based Estimates of the Effects of Efavirenz on Bedaquiline Pharmacokinetics and Suggested Dose Adjustments for Patients Coinfected with HIV and Tuberculosis. Antimicrob Agents Chemother. 2013;57(6):2780–7.
[6] Svensson EM, Dooley KE, Karlsson MO. Impact of Lopinavir-Ritonavir or Nevirapine on Bedaquiline Exposures and Potential Implications for Patients with Tuberculosis-HIV Coinfection. Antimicrob Agents Chemother. 2014;58(11):6406–12.
[7] Svensson EM, Murray S, Karlsson MO, Dooley KE. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. J Antimicrob Chemother. 2015;70(4):1106–14.
[8] Brill MJE, Svensson EM, Pandie M, Maartens G, Karlsson MO. Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug resistant tuberculosis. Abstract submitted to PAGE 2016.
[9] Svensson EM, Dosne A-G, Karlsson MO. Population pharmacokinetics of bedaquiline and metabolite M2 in drug-resistant tuberculosis patients – the effect of time-varying weight and albumin. Submitted.
[10] Dosne A-G, Bergstrand M, Karlsson MO. Application of Sampling Importance Resampling to estimate parameter uncertainty distributions. PAGE 22 (2013) Abstr 2907 [www.page-meeting.org/?abstract=2907]; Glasgow, Scotland.
[11] Chigutsa E, Patel K, Denti P, Visser M, Maartens G, Kirkpatrick CMJ, et al. A time-to-event pharmacodynamic model describing treatment response in patients with pulmonary tuberculosis using days to positivity in automated liquid mycobacterial culture. Antimicrob Agents Chemother. 2013;57(2):789–95.

Acknowledgement

The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement n°115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Disclosure

MK has received research grants from Janssen pharmaceuticals.

C-02: *Solène Desmée* Joint modelling for nonlinear longitudinal PSA kinetics and survival data in metastatic prostate cancer patients

Solène Desmée (1,2), France Mentré (1,2), Christine Veyrat-Follet (3), Bernard Sébastien (4) and Jérémie Guedj (1,2)

(1) INSERM, IAME, UMR 1137, F-75018, Paris, France (2) Université Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, F-75018, Paris, France (3) Drug disposition, Disposition Safety and Animal Research Department, Sanofi, Bridgewater, USA (4) Biostatistics and Programming, Sanofi, Chilly-Mazarin, France

Introduction

Since its introduction, serum prostate specific antigen (PSA) is massively used in the screening, the management and the response to treatment of prostate cancer. However there is no general consensus on the relevance of PSA for prediction of disease evolution and survival, in particular in patients with advanced cancer. The lack of consensus might be partly related to the use of some specific aspects of the PSA trajectory, such as doubling time or nadir value during treatment, and not of all the kinetic information available, in the evaluation of the PSA predictive ability. A more sophisticated approach is to use a joint model, which characterizes simultaneously the entire kinetics of a biomarker and its impact on a time-to-event [1,2].

Objectives

The objectives of this PhD thesis were the following:

1. To compare by simulation the precision of parameters obtained using joint and two-stage approaches when PSA kinetics is described by a nonlinear mixed-effect model (NLMEM) using the SAEM algorithm implemented in Monolix

2. To characterize on real data the relationship between PSA kinetics and survival in metastatic castration-resistant prostate cancer (mCRPC) patients treated by docetaxel

3. To evaluate the predictability on survival of Bayesian individual dynamic predictions of PSA kinetics

Methods

Data came from one arm of a phase 3 clinical trial [3]. In this study 596 mCRPC men were treated by docetaxel, the reference chemotherapy, and PSA had to be measured every 3 weeks during treatment, then every 12 weeks until the end of study, when vital status was collected. For the sake of internal validation, the dataset was randomly split into a training sample and a validation sample of 400 and 196 patients, respectively.

1. We performed a clinical trial simulation to compare joint and two-stage approaches. PSA kinetics was described by a biexponential model with parameter values inspired from the real data. 100 samples with 500 patients were simulated using the R software with PSA measurements every 3 weeks for 2 years. The survival model was a Weibull proportional hazard model with increasingly high levels of association between the current PSA kinetics and survival. Using the SAEM algorithm, parameters estimation using joint approach was compared in terms of bias, type 1 error and power to two-stage approach which consists in fitting the PSA data using a NLMEM then inserting the obtained individual longitudinal parameters into a survival model [4].

2. To analyze the training sample, we developed a mechanistic joint model. The PSA kinetic model relied on 3 ordinary differential equations (ODEs) and assumed that PSA is produced by two types of cells, namely treatment-sensitive cells and -resistant cells, on which docetaxel has no effect [5]. Several survival models relying on functions of ODE outputs, such as PSA kinetics or number of resistant cells, were compared using the Bayesian Information Criterion (BIC). Model evaluation was based on individual weighted residuals

(IWRES) and on Cox-Snell and Martingale residuals for longitudinal and survival parts, respectively. Model prediction was assessed on the validation sample.
3. We focused on the possibility to predict survival in a new patient of the validation sample based on his individual PSA kinetics and assuming that the model and the population parameters are known and used as priors. Thus the PSA observations of the new patient were assumed to be available until a landmark time s (if the patient is still alive) and we aimed to predict the conditional probability of survival up to the prediction horizon s+t with t>0. To take into account the individual estimation uncertainty [6], for each patient of the validation sample and each $s \in \{0,3,6,12,18\}$ months, we drew 200 Monte-Carlo samples of individual parameter using the STAN software [7] and computed 200 PSA trajectories and survival functions. This procedure provided individual dynamic predictions of PSA evolution and survival with 95% prediction intervals using the 2.5% and 97.5% simulated percentiles. Model discrimination and calibration were assessed using time-dependent area under the ROC curve (AUC), Brier Score (BS) and scaled BS (sBS) [8–10] along with Monte-Carlo confidence intervals.

Results
1. As described in detail in [11], we found that estimation with the correct joint models provided small biases regardless of the association between PSA and survival. Inversely the two-stage approach led to increasingly high level of bias when the association increased. In particular there was a systematic underestimation of the PSA effect on survival. Type 1 error, i.e., the probability to detect an effect of PSA on survival when there is none, was equal to 4 and 12% for joint and two-stage approaches, respectively. Power was 100% for the two methods.
2. The mechanistic nature of the model allowed us to consider other markers for survival that are not observed. Thus a joint model relying on the non-observed number of both resistant and sensitive cells led to the lowest BIC. No misspecification was revealed by residuals. The relevance of this model, instead of a model relying on the sole PSA, was reinforced by the fact that it could be used to correctly predict the survival curve of the validation sample using only PSA measurements.
3. This approach allowed to plot for each new patient individual dynamic predictions of PSA evolution and survival with prediction intervals which got wider when the horizon t increased, and shrank when s increased. Using the AUC, BS and sBS, we showed that joint modelling, provided that PSA kinetics is observed for at least 6 months ($s>6$), could identify the most-at-risk patients and precisely predict their survival in the next 12 months (i.e., $t<12$).

Conclusion
Our work investigated the use of mechanistic nonlinear joint models to predict the survival in patients with mCRPC treated by docetaxel. SAEM algorithm implemented in Monolix was shown by simulation to provide precise estimates for nonlinear joint models. When used on real data, a model accounting for the kinetics of both docetaxel-resistant and -sensitive cells provided a better fit to the data than a model relying on the sole PSA kinetics. Lastly we showed how this approach could be used in personalized medicine to prospectively predict patient's survival using STAN to get the full conditional distribution and using new metrics for evaluation of predictability. Time-dependent discrimination and calibration metrics allowed to define predictive capacities of the joint model according to landmark time and prediction horizon. This work opens the way for the use of more complex and physiological joint models that could incorporate other relevant biomarkers to improve treatment evaluation and predictions in prostate cancer.

Acknowledgements:
The authors would like to thank the Drug Disposition Department, Sanofi, Paris, which supported Solène Desmée by a research grant during this work.

References:
[1] Tsiatis AA, Davidian M. Joint modeling of longitudinal and time-to-event data: an overview. Stat. Sin. 2004;14:809–34.
[2] Rizopoulos D. Joint Models for Longitudinal and Time-to-Event Data: With Applications in R. CRC Press; 2012.
[3] Tannock IF, Fizazi K, Ivanov S, Karlsson CT, Fléchon A, Skoneczna I, et al. Aflibercept versus placebo in

combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. Lancet Oncol. 2013;14:760–8.
[4] Ibrahim JG, Chu H, Chen LM. Basic Concepts and Methods for Joint Models of Longitudinal and Survival Data. J. Clin. Oncol. 2010;28:2796–801.
[5] Seruga B, Ocana A, Tannock IF. Drug resistance in metastatic castration-resistant prostate cancer. Nat. Rev. Clin. Oncol. 2011;8:12–23.
[6] Rizopoulos D. Dynamic Predictions and Prospective Accuracy in Joint Models for Longitudinal and Time-to-Event Data. Biometrics. 2011;67:819–29.
[7] Stan Development Team. Stan Modeling Language Users Guide and Reference Manual, Version 2.8.0. 2015.
[8] Graf E, Schmoor C, Sauerbrei W, Schumacher M. Assessment and comparison of prognostic classification schemes for survival data. Stat. Med. 1999;18:2529–45.
[9] Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiol. Camb. Mass. 2010;21:128–38.
[10] Blanche P, Proust-Lima C, Loubère L, Berr C, Dartigues J-F, Jacqmin-Gadda H. Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. Biometrics. 2015;71:102–13.
[11] Desmée S, Mentré F, Veyrat-Follet C, Guedj J. Nonlinear Mixed-Effect Models for Prostate-Specific Antigen Kinetics and Link with Survival in the Context of Metastatic Prostate Cancer: a Comparison by Simulation of Two-Stage and Joint Approaches. AAPS J. 2015;17:691–9.

C-03: *Stein Schalkwijk* A physiologically-based population pharmacokinetic analysis to assess a lower efavirenz dose of 400 mg once daily in HIV-infected pregnant women.

Stein Schalkwijk (1,2), Rob ter Heine (1), Angela Colbers (1), Alwin Huitema (3), Paolo Denti (4), Kelly E. Dooley (5), Edmund Capparelli (6), Brookie Best (6), Tim Cressey (7,8), Rick Greupink (2), Frans GM Russel (2), Mark Mirochnick (9), and David Burg

(1) Department of Pharmacy, Radboud University Medical Centre, Nijmegen, The Netherlands; (2) Department of Pharmacology & Toxicology, Radboud University Medical Centre, Nijmegen, The Netherlands; (3) Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, The Netherlands; (4) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa; (5) Johns Hopkins University School of Medicine, Baltimore, Maryland; (6) UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences & School of Medicine, University of California San Diego; (7) Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand; (8) Harvard School of Public Health, Boston, MA, USA; (9) Boston University, Boston, MA, USA

Background:

Globally, efavirenz (EFV) is a cornerstone for the treatment of HIV infection. There is interest in exploring lower EFV doses, in part to avoid toxicities, but largely to reduce health program costs, with the goal of universal access to treatment. It has been shown that 400mg once-daily (QD) was non-inferior to the standard dose of 600mg QD in adults with regards to virologic response.(1) During pregnancy, the pharmacokinetics (PK) of antiretrovirals may be altered due to changes in protein binding, volume of distribution, and/or clearance, potentially leading to sub-therapeutic exposure and consequently a higher risk of treatment failure, drug resistance, and HIV transmission to the neonate.(2) Currently, it is unknown whether the 400mg dose is also appropriate for pregnant women. Pharmacokinetic studies have been performed to investigate the clinical relevance of pregnancy on the PK of EFV but no studies have investigated the lower 400mg dose. Moreover, large variability because of CYP2B6 polymorphisms influencing EFV clearance can make inference challenging.(3-7)

Objectives:

- To develop a physiologically-based (PB) population PK model to describe the PK of EFV in HIV-infected pregnant and non-pregnant women using the largest dataset yet available

- To simulate EFV exposure (C_{12}) using 600mg and 400mg QD during third trimester of pregnancy.

Methods:

PK data of pregnant and non-pregnant women taking EFV were collected from several clinical trials.(5, 7-13) Patients using potentially interacting concomitant medicines (e.g. rifampicin or isoniazid) were excluded. Population pharmacokinetic modeling was performed with NONMEM 7.3 with FOCE-I.(14)

To account for the relation between hepatic systemic and first-pass metabolism, a well-stirred liver model [eq.1] was implemented.(15)

$$CL_{hep}=Q_{hep,plasma}*CL_{int,hep}*f_u/(Q_{hep,plasma}+CL_{int,hep}*f_u) \text{ [eq.1]}$$

Hepatic clearance (CL_{hep}) is expressed as a function of hepatic plasma flow ($Q_{hep,plasma}$), intrinsic hepatic clearance ($CL_{int,hep}$), and fraction unbound (f_u). A pregnancy-induced increase in $Q_{hep,plasma}$ [eq.2] and decrease in f_u [eq.3] were included, *a priori*.

$Q_{hep,plasma}=(1-Ht)*Q_{hep}$ [eq.2]

$f_u=K_D/(K_D+[P])$ [eq.3]

Hepatic blood flow (Q_{hep}) and EFV protein (albumin)-binding dissociation constant (K_D) were fixed to reported values.(16, 17) Polynomial relations (validated for use in PBPK models) between gestational age (GA) and albumin concentrations (P) [eq.4] and hematocrit values (Ht) [eq.5] were used to predict pregnancy-induced changes in f_u and $Q_{hep,plasma}$, respectively.(18, 19)

$[P(\mu M)]=(45.8-0.1775*GA-0.0033*GA^2)/0.07$ [eq.4]

$[Ht(\%)]=39.1-0.0544*GA-0.0021*GA^2$ [eq.5]

Flow parameters (^0.75) and volumes (^1) were allometrically scaled to a non-pregnant body weight of 70 kg. Additionally, pregnancy was tested as covariate (dichotomous) on all PK parameters. This effect was retained in the model when inclusion was statistically significant ($\Delta OFV \geq 3.84$; $p \leq 0.05$), clinically relevant (>10% change) and physiologically plausible. Prediction-corrected visual predictive checks and routine goodness-of-fit plots were assessed throughout the model building process.(20)

Mid-dose concentrations (~C_{12}) of <1.0 mg/L were previously related to treatment failure.(21) Therefore, the final model was used to simulate (1000x/condition) total and unbound C_{12} for 600mg and 400mg QD in pregnant (GA 38 weeks) and non-pregnant women.

Results:

PK profiles were available from 253 HIV-infected women (1699 samples). Paired observations during pregnancy (642) and non-pregnant (466) were available from 79 women. Median (IQR) non-pregnant weight was 59 (52-68) kg. Median (range) GA was 35 (25-39) weeks. A 2-compartment disposition model with first-order elimination and 3 absorption transit compartments best described the data. Data on CYP2B6 genotype (c.516G>T) in our population were limited (18%). A mixture model was implemented to account for the multi-modal distribution of CL_{int} as a result of CYP2B6 polymorphisms by imputing the missing CYP2B6-related phenotypes; slow (SM), intermediate (IM) and fast (FM) metabolizers.(22) Stochastic simulation and estimation showed that the population frequencies of the mixture could not be identified; therefore population frequencies were fixed to 12, 36 and 52% for the SM, IM and FM, respectively, based on available data on race or region combined with known prevalence of the CYP2B6 genotypes.(23, 24) Final population estimates (reference 70kg) of EFV Ktr, $CL_{int,SM}/F$, $CL_{int,IM}/F$, $CL_{int,FM}/F$, Vc/F, Q/F and Vp/F were 1.7 1/h, 1300 L/h, 3080 L/h, 4410 L/h, 116 L, 35 L/h, and 403 L, respectively. Inter-individual variability was 32% and 47% for CL_{hep} and Ka, respectively. Inter-occasion variability was 26% for pre-hepatic bioavailability. The residual proportional error was 18%. CL_{hep} was increased with 32%, 30%, and 28% at 38 weeks of gestation compared to non-pregnant for SM, IM, and FM. Pregnancy had no effect on CL_{int}. Moreover, pregnancy was not a significant and relevant covariate for Ktr, Q, Vc and Vp.

For EFV 600mg QD, the simulated median (IQR) steady-state C_{12} in non-pregnant women were 6.59 (4.63-9.03), 2.53 (1.78-3.56), and 1.80 (1.28-2.54) mg/L for SM, IM, and FM, respectively. In pregnant women the predicted C_{12} were 4.92 (3.46-6.88), 1.83 (1.27-2.65), and 1.35 (0.90-1.96) mg/L. For 400mg QD, the predicted C_{12} in non-pregnant women were 4.37 (3.17-6.07), 1.74 (1.24-2.32), and 1.17 (0.84-1.64) mg/L for SM, IM and FM, respectively, as opposed to 3.22 (2.23-4.57), 1.26 (0.92-1.75), and 0.82 (0.58-1.20) mg/L during pregnancy. Although this apparent decrease in total concentration indicates sub-therapy, it should be noted that the predicted unbound concentrations were not altered (<2%) by pregnancy.

Conclusions:

Pregnancy decreases total EFV C_{12} but unbound EFV concentrations are predicted to be unchanged. Although this finding warrants *in-vivo* confirmation, it indicates that a dose reduction to 400mg is feasible.

Discussion**:** As unbound EFV concentrations were not directly measured in the studies used for this analysis the absence of an effect of pregnancy on unbound concentrations must be confirmed. Nevertheless, the PB approach used in this study suggests that the lower EFV dose might be adequate during late pregnancy, a finding that may have been missed with empirical modeling of total concentrations. The current study uses the largest set of EFV PK data of pregnant and non-pregnant HIV-infected women compiled to date. We were able to differentiate between metabolic phenotypes and used a PB approach to account for pregnancy-induced alterations in f_u and $Q_{hep,plasma}$. Pregnancy was not identified as an additional covariate for $CL_{int,hep}$. This indicates no or minor pregnancy-related induction of metabolic enzymes involved in EFV metabolism (e.g. CYP2B6). Of note, pregnancy-related induction of CYP2B6 has been suggested but was not confirmed *in vivo*.(25)

References:

[1] Group ES. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014.
[2] Gilbert EM, Darin KM, Scarsi KK, McLaughlin MM. Antiretroviral Pharmacokinetics in Pregnant Women. Pharmacotherapy. 2015.
[3] Naidoo P, Chetty VV, Chetty M. Impact of CYP polymorphisms, ethnicity and sex differences in metabolism on dosing strategies: the case of efavirenz. Eur J Clin Pharmacol. 2014;70(4):379-89.
[4] Olagunju A, Bolaji O, Amara A, Else L, Okafor O, Adejuyigbe E, et al. Pharmacogenetics of pregnancy-induced changes in efavirenz pharmacokinetics. Clin Pharmacol Ther. 2015;97(3):298-306.
[5] Dooley KE, Denti P, Martinson N, Cohn S, Mashabela F, Hoffmann J, et al. Pharmacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis coinfection. J Infect Dis. 2015;211(2):197-205.
[6] Bartelink IH, Savic RM, Mwesigwa J, Achan J, Clark T, Plenty A, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in Tororo, Uganda. J Clin Pharmacol. 2014;54(2):121-32.
[7] Cressey TR, Stek A, Capparelli E, Bowonwatanuwong C, Prommas S, Sirivatanapa P, et al. Efavirenz pharmacokinetics during the third trimester of pregnancy and postpartum. J Acquir Immune Defic Syndr. 2012;59(3):245-52.
[8] Boyd MA, Siangphoe U, Ruxrungtham K, Duncombe CJ, Stek M, Lange JM, et al. Indinavir/ritonavir 800/100 mg bid and efavirenz 600 mg qd in patients failing treatment with combination nucleoside reverse transcriptase inhibitors: 96-week outcomes of HIV-NAT 009. HIV medicine. 2005;6(6):410-20.
[9] Van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet. 2004;363(9417):1253-63.
[10] Semvua HH, Mtabho CM, Fillekes Q, van den Boogaard J, Kisonga RM, Mleoh L, et al. Efavirenz, tenofovir and emtricitabine combined with first line tuberculosis treatment in TB-HIV-coinfected Tanzania patients: a pharmacokinetic and safety study. Antivir Ther. 2012.
[11] Kappelhoff BS, Huitema AD, Yalvac Z, Prins JM, Mulder JW, Meenhorst PL, et al. Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. ClinPharmacokinet. 2005;44(8):849-61.
[12] Pharmacokinetic Study of Antiretroviral Drugs and Related Drugs During and After Pregnancy. Available from: https://clinicaltrials.gov/ct2/show/NCT00042289.
[13] Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women. (PANNA). Available from: https://clinicaltrials.gov/ct2/show/NCT00825929.
[14] Bauer RJ. NONMEM USERS GUIDE INTRODUCTION TO NONMEM 7.3.0. ICON Development Solutions, 2014.
[15] Gordi T, Xie R, Huong NV, Huong DX, Karlsson MO, Ashton M. A semiphysiological pharmacokinetic model for artemisinin in healthy subjects incorporating autoinduction of metabolism and saturable first-

pass hepatic extraction. Br J Clin Pharmacol. 2005;59(2):189-98.
[16] Avery LB, Bakshi RP, Cao YJ, Hendrix CW. The male genital tract is not a pharmacological sanctuary from efavirenz. Clin Pharmacol Ther. 2011;90(1):151-6.
[17] Nakai A, Sekiya I, Oya A, Koshino T, Araki T. Assessment of the hepatic arterial and portal venous blood flows during pregnancy with Doppler ultrasonography. Archives of gynecology and obstetrics. 2002;266(1):25-9.
[18] Abduljalil K, Furness P, Johnson TN, Rostami-Hodjegan A, Soltani H. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. Clin Pharmacokinet. 2012;51(6):365-96.
[19] Avery LB, Sacktor N, McArthur JC, Hendrix CW. Protein-free efavirenz concentrations in cerebrospinal fluid and blood plasma are equivalent: applying the law of mass action to predict protein-free drug concentration. Antimicrob Agents Chemother. 2013;57(3):1409-14.
[20] Svensson E, van der Walt JS, Barnes KI, Cohen K, Kredo T, Huitema A, et al. Integration of data from multiple sources for simultaneous modelling analysis: experience from nevirapine population pharmacokinetics. Br J Clin Pharmacol. 2012;74(3):465-76.
[21] Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15(1):71-5.
[22] Keizer RJ, Zandvliet AS, Beijnen JH, Schellens JH, Huitema AD. Performance of methods for handling missing categorical covariate data in population pharmacokinetic analyses. The AAPS journal. 2012;14(3):601-11.
[23] Rotger M, Tegude H, Colombo S, Cavassini M, Furrer H, Decosterd L, et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther. 2007;81(4):557-66.
[24] Sukasem C, Cressey TR, Prapaithong P, Tawon Y, Pasomsub E, Srichunrusami C, et al. Pharmacogenetic markers of CYP2B6 associated with efavirenz plasma concentrations in HIV-1 infected Thai adults. Br J Clin Pharmacol. 2012;74(6):1005-12.
[25] Dickmann LJ, Isoherranen N. Quantitative prediction of CYP2B6 induction by estradiol during pregnancy: potential explanation for increased methadone clearance during pregnancy. Drug Metab Dispos. 2013;41(2):270-4.

C-06: *Matts Kågedal* Time-to-Event Modeling of Peripheral Neuropathy – Platform Mega-Analysis of Eight vc-MMAE Antibody-Drug Conjugates (ADCs)

Matts Kågedal (1), Divya Samisen (1), Bill Gillespie (2), Dan Lu (1), Bernard Fine (1), Y J Choi (1), Chunze Li (1), Sandhya Girih (1), Jin Yan Jin (1)
(1) Genentech, Inc., South San Francisco, CA. (2) Metrum institute, Tariffville, CT

Objectives: valine-citrulline-MMAE (vc-MMAE) ADCs are the most commonly used linker-drug combinations in the ADC platform currently under clinical investigation. Peripheral neuropathy (PN) was one of the adverse effects frequently observed in clinical studies with vc-MMAE ADCs resulting in treatment discontinuation, thereby limiting the duration of treatment with these ADCs. The objective of the this analysis was to develop a pan-ADC PN model to describe the exposure-response (E-R) and the risk factors associated with PN in support of the clinical development of the vc-MMAE ADCs.

Methods: A time-to-event (TTE) parametric survival model to the onset of PN grade ≥ 2 events across multiple vc-MMAE ADCs was developed using NONMEM® 7 to describe the relationship between the conjugate analyte exposure and the incidence of PN. Data from phase I and II studies across the tested dose ranges of 0.1-3.2 mg/kg were included in the analysis. In this model, hazard is a function of the drug concentration in a hypothetical effect compartment, time and potential PN risk factors such as demographics (age, body size metrics, gender), prior chemotherapy, prior incidence of PN, diabetes, malignancy type, ADC type and albumin. The model performance was verified by comparison of observed PN event to events generated by simulation from the model by the use of visual predictive checks.

Results: The developed TTE model successfully predicted the time course of the PN incidence for the individual ADCs tested across multiple oncology indications. The model described the exposure-response across a range of tested doses across the individual ADCs. Covariate analysis identified body weight as a statistically significant risk factor for PN. A trend of higher risk of peripheral neuropathy was observed in patients with higher body weight even after accounting for exposure. The difference between the ADCs in terms of PN risk was minimal after accounting for differences in the exposure, treatment duration and body weight. No significant influence of additional pre-disposing risk factors on the incidence of PN was identified.

Conclusions: The cross-molecule mega-analysis demonstrates the utility of using a pan-ADC model-based approach to characterize the incidence of PN for patients dosed with vc-MMAE ADCs. Such platform model could be used to simulate different dosing scenarios to inform dose strategy for vc-MMAE ADCs.

C-07: *Lucy Hutchinson* Mixed-effect modelling of transient tumour growth dynamics following anti-angiogenic therapy

L G Hutchinson (1), E A Gaffney (1), P K Maini (1), J Wagg (2), A Phipps (3), H J Mueller (4), H M Byrne (1), B Ribba (2)

(1) Wolfson Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Andrew Wiles Building, Radcliffe Observatory Quarter, UK (2) Roche Pharmaceutical Research and Early Development, Clinical Pharmacology, Roche Innovation Centre Basel, Switzerland (3) Roche Pharmaceutical Research and Early Development, Clinical Pharmacology, Roche Innovation Centre Welwyn, UK (4) Roche Pharmaceutical Research and Early Development, Roche Innovation Centre Penzberg, Germany

Objectives: Anti-angiogenic (AA) therapy may give rise to a transient period where tumour blood vessels are less permeable and tortuous, and the tumour is better perfused [1][2]. Experimental evidence suggests that the efficacy of radiotherapy and chemotherapy may be enhanced during this period [3][4]. Identification of the timing of the normalization window could enable optimal design of combination therapy regimen.

Our objective is to characterize the vessel normalization window leveraging only tumour volume (TV) data in preclinical models treated with bevacizumab (BEV) and vanucizumab (VAN). To conclude, we simulate tumour response to a hypothetical cytotoxic drug administered inside and outside the inferred window.

Methods: BEV is an anti-VEGF antibody and VAN is a bispecific anti-VEGF/anti-Ang2 antibody. KPL-4 xenografted mice were randomized into control, BEV, and VAN treatment groups with n=10 per group. Each group received 5 weekly doses and tumour size measurements were taken twice per week.

We draw inspiration from seminal and recent models of tumour growth kinetics with and without AA therapies [5][6][7][8]. In our model, we assume that TV undergoes logistic growth with a dynamic carrying capacity proportional to vascular volume.

We assume that the normalized vasculature transiently improves delivery of oxygen and nutrients, enhancing tumour growth via an increased carrying capacity. For model selection and fitting, we used Monolix for a mixed effects approach that leverages TV data. For model selection we compared the Bayesian Information Criterion (BIC) for each model, alongside visual predictive checks (VPC) and residual standard error (RSE) of population parameters and inter-individual variability (IIV).

Results: A model accounting for a transient period during which vessels deliver more oxygen and nutrients to the tumour describes the data well, as evidenced by diagnostic plots such as VPC and RSE<30% for population parameters and RSE<50% for IIV parameters.

Our simulations of the administration of a hypothetical cytotoxic drug show that the drug is more efficacious if administered during the transient window, leading to a greater reduction in TV than when it is administered outside the transient window.

Conclusions: Mixed effects modelling can be used to locate and parameterise the window of enhanced tumour growth, which may be a direct or indirect effect of the vessel normalization window, for KPL-4 xenografts leveraging only TV data. Our model predicts that cytotoxic therapy would be more efficacious if administered within the transient window.

References:

[1] Winkler F et al. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. Cancer cell 6(6), 553–63 (2004).

[2] Dings RPM et al. Scheduling of radiation with angiogenesis inhibitors anginex and Avastin improves therapeutic outcome via vessel normalization. Clinical cancer research : an official journal of the American Association for Cancer Research 13(11), 3395–402 (2007).

[3] Myers AL, Williams RF, Ng CY, Hartwich JE & Davidoff AM. Bevacizumab-induced tumor vessel remodeling in rhabdomyosarcoma xenografts increases the effectiveness of adjuvant onizing radiation. Journal of pediatric surgery 45(6), 1080–5 (2010).

[4] Dickson PV et al. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered Chemotherapy. Clinical Cancer Research 13(13), 3942–3950 (2007).

[5] Simeoni M. et al. Predictive Pharmacokinetic-Pharmacodynamic Modeling of Tumor Growth Kinetics in Xenograft Models after Administration of Anticancer Agents. Cancer Research 64(3), 1094–1101 (2004). ?

[6] Rocchetti M et al. Predictive pharmacokinetic-pharmacodynamic modelling of tumor growth after administration of an anti-angiogenic agent, bevacizumab, as single-agent and combination therapy in tumor xenografts. Cancer chemotherapy and pharmacology 71(5), 1147–57 (2013). ?

[7] Wilson S et al. Modeling and predicting optimal treatment scheduling between the antiangiogenic drug sunitinib and irinotecan in preclinical settings. CPT: Pharmacometrics & Systems Pharmacology (2015).

[8] Ouerdani A, Struemper H, Suttle A, Ouellet D & Ribba B. Preclinical Modeling of Tumor Growth and Angiogenesis Inhibition to Describe Pazopanib Clinical Effects in Renal Cell Carcinoma. CPT: Pharmacometrics & Systems Pharmacology (2015).

C-08: *Maria Luisa Sardu* Modelling of classified individual tumor lesions in metastatic colorectal cancer (mCRC) patients using delay differential equations.

M.L. Sardu (1), N. Terranova (1), P. Girard (1), A. Munafo (1)
Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland

Objectives: Standard practice in pharmacometrics applied to oncology since publication of the Claret's paper [1] has been to model the relationship between drug exposure and total individual tumor size, which can hide valuable information contained in individual target lesions (iTL) dynamics. In particular, non-identical dynamics of individual lesions, belonging to separate tumor tissues, might explain differences in resistance to anti-tumor drugs [2]. A new method proposed to automatically classify iTL and to measure the degree of similarity in their dynamics showed that iTL can be "desynchronized" [2]. Hence, we propose a model-based approach to assess the applicability of delay differential equations (DDE) [3] to describe the delayed dynamics of iTL within patients (pts).

Methods: In a recent work based on a non-parametric methodology applied to multiple classified iTL [2], it was found that the degree of similarity in lesion dynamics increases when accounting for some delay between different tissues. Following this rationale, we propose here a model-based approach to describe the dynamics of classified iTL, accounting for inter-lesion variability [4] in delays. We first applied the tumor size model proposed by Claret et al [1, 5] to classified iTL and, resorting to DDE, we then introduced delayed terms on the state variables describing either tumor growth or the killing rate. As the model variants (i.e., including the delayed term) are nested to the original Claret one, the comparison was based on the objective function values and the standard model diagnostics.
Data from one phase II study in mCRC pts were analyzed. For each classified tumor tissue, longitudinal measurements of the sum of the product (area) of longest diameters were considered.
The analyses were performed using Monolix 4.3.3.

Results: Data from 902 mCRC pts with 1316 classified iTL [2] (579 pts with 1 lesion, 245 pts with 2, 67 with 3, 9 with 4, and 2 with 5 lesions) and a total of 3705 observations (measurements), were analyzed. Overall, the three models were able to describe the available data. However, the DDE model with delayed term applied to the killing rate was found the most suitable in describing the classified iTL data.

Conclusions: Given that iTL dynamics might not be synchronized, DDE appears to be a valuable tool in the investigation of the mechanism of potential drug resistance and in the description of the tumor growth dynamics in different tissues.

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

References:
[1] Claret L. et al., Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. Journal of Clinical Oncology (2009) 27(25): 4103-4108.
[2] Terranova N. et al., Analysis of individual target lesions for tumor size models of drug resistance: a new methodology encompassing signal processing and machine learning. PAGE 24 (2015) Abstr 3399 [www.page-meeting.org/?abstract=3399]
[3] Koch G. et al., Modeling of delays in PKPD: classical approaches and a tutorial for delay differential equations. Journal of pharmacokinetics and pharmacodynamics (2014) 41(4): 291-318.
[4] Schindler E. et. al., PKPD-Modeling of individual lesion Standardized Uptake Value (SUV) in Gastro-

Intestinal Stromal Tumors (GIST) patients treated with sunitinib. PAGE 23 (2014) Abstr 3210 [www.page-meeting.org/?abstract=3210]
[5] Girard P. et al., Drug-disease model of tumor size and overall survival in metastatic colorectal cancer patients treated with cetuximab administered weekly or every second week. European Journal of Cancer (2013) Vol. 49.

C-10: *Robert Bauer* An overview of Estimation-Maximization Algorithms Used in Population Analysis Methods

Robert J. Bauer
ICON plc, Gaithersburg, MD

Objectives:
To present an overview of expectation-maximization algorithms used to analyse pharmacokinetic/ pharmacodynamics models for population data. Their statistical basis will be briefly discussed, with emphasis on practical suggestions as to when and how to use them.

Overview:
Over the last thirty years, a series of algorithms for PK/PD modelling and population analysis have become available to the pharmaceutical scientist to solve what are called non-linear mixed effects models. The statistical goal of these tools is to find the best fitting set of population parameters that fit the entire population of data, taking into consideration all possible values of individual parameters.

The first algorithms to be developed for population analysis of PK/PD data were the first order methods for normally distributed data, which use first order approximations to simplify the otherwise daunting task of this statistical analysis problem. These methods are reasonable when residual variance within subjects is small, and/or the non-linearity of parameter distribution of the PK/PD model is not large. For additional accuracy, and useful for non-normally distributed data, higher order approximation methods such as Laplace and Gaussian quadrature were developed, but require more computation time and can be unstable for complex problems.

To reduce the bias and computational cost in the analysis resulting from imposing a linear or higher-order approximation, Monte Carlo expectation maximization (EM) methods were developed. The Monte Carlo methods are particularly useful for efficient analysis of complex PK/PD models, and provide robust and accurate analyses for conditions that cause high non-linearity (non-normality) in the individual parameter distributions, such as very sparse data (few data points per subject) or categorical and other non-normally distributed data.

There are several algorithms and variants of these EM methods. The importance sampling algorithm samples the important regions of the posterior density to obtain weighted conditional means and variances of individual parameters, which are then used to efficiently update values of population parameters and population variances. A variant of the importance sampling uses a quasi-random sampling (Sobol) sequence, called quasi-random parametric expectation-maximization (QRPEM), which can reduce the stochastic variability in the results, thus requiring fewer random samples for a given desired noise level limit. As the data becomes more sparse (fewer data points per subject), or for large numbers of data below the quantifiable limit of the assay, or the observed data is non-normally distributed such as with categorical data, the importance sampler should be adjusted with increasing number of samples, expanding the variance of the importance sampler relative to the variance of the posterior density (lowering the effective acceptance rate), and/or using a t-distribution sampler with low degrees of freedom, to obtain more samples near the elongated tails of the posterior distribution.

The stochastic approximation EM (SAEM) algorithm uses a Markov-Chain Monte Carlo sequence of samples to sample the posterior density. Instead of staying in one place as the importance sampler does, the

sampler travels throughout the region of posterior density, collecting and accepting many samples in regions where the goodness of fit to the individual parameters is high, and collecting and accepting few samples where the goodness of fit is low. As the data becomes more sparse (fewer data points per subject), or for large numbers of data below the quantifiable limit of the assay, or the observed data is non-normally distributed such as with categorical data, the SAEM method should be adjusted with increasing number of samples collected for each individual.

C-11: *Brian Corrigan* Announcement of ACoP7

Brian Corrigan
ISoP

ACoP7 is shaping up to be the most comprehensive ACoP to date! We hope that you will be able to join us October 23rd - 27th in Bellevue (Eastside Seattle) Washington. The ACoP7 program includes 17 symposia with lectures on a wide-range of topics including quantitative systems pharmacology (QSP), physiologically based pharmacokinetic (PBPK) modeling, PKPD and dose response analyses, advances in model building approaches, in vitro in vivo correlation (IVIVC), as well as application of pharmacometrics in drug development to inform decision making and optimize dose finding studies. (ACoP7 Program)

Some highlights of the ACOP7 meeting.

Dedicated Pediatric Pre-Conference: "What is the Role of Clinical Pharmacology and Pharmacometrics in Bringing New Medicines to this Special Population" this day long meeting will highlight the challenges in pharmacometrics session will feature innovative talks. It will also feature a pediatric themed poster session.

Keynote Speaker, Malcolm Rowland: Pharmacokinetics: "Reflections and the Big Picture"

State-of-the-Art Lecturer, Jaime Caro: "DICE Simulation: a shotgun marriage or wedded bliss for pharmacometrics and pharmacoeconomics?"

QSP Track: For the QSP community, this year will feature concurrent sessions with a QSP-theme throughout the entire meeting. There will also be a special Open Forum session on **'Making QSP Happen: Strategies and Lessons Learned from Experts Who've Done It'** sponsored by ISoP QSP Special Interest Group (SIG). Attendees will also have the opportunity to meet the leadership of the QSP SIG. and new for 2016, we will add a Student Award sponsored by QSP-SIG.

Statistics/Pharmacometrics Interest Group Topics: This year, ISOP has initiated a joint SIG with the American Statistical Association related to topics of mutual interest. You will have the opportunnity to meet with members of the SIG to discuss ideas around issues and topics of common interest in these closely aligned quantitative fields. There will also be a special joint SIG-endorsed session entitled "**Evaluation and optimization of dose finding studies".**

Highlighting the Best submitted works in our session: Based on your feedback, we have added an opportunity to highlight abstracts identified as outstanding as oral presentations in individual sessions.

Students: Students make up nearly a quarter of our attendees, and we have created unique opportunities throughout the meeting for students to network with their peers and to learn new skills. This year will feature both student-specific luncheons, as well as new student-specific training tutorials. With a deeply discounted registration for students, ACoP7 offers a unique opportunity for students to both learn new skills and to network.

Open Science and Consortia Approaches: This year's meeting will feature a tutorial focused on raising awareness of various consortia that are ongoing in our field. It will also mark the start for planning of open-

Science Communities of Practice within ISoP, including plans for ISoP to work with the Critical Path Institute.

Standards and Best Practices: Come meet with the Standards and Best Practices Committee to learn about all the ongoing work that ISoP is undertaking to set standards for data preparation and for model evaluation.

Vendor Workshops and Exhibits: There will be vendor sponsored workshops, presentations, posters and exhibits demonstrating the latest updates in tools and technologies.

Global Attendance: Last year we welcomed attendees from 23 countries. Take this chance to network with friends and colleagues from across the globe. By clicking on the secured link below, you will be able to enter your information and reserve your spot at this scientific event for professionals dedicated to furthering the disciplines in Pharmacometrics.

Abstract submission is also open (deadline of June 15) in addition to application for our new Student Award sponsored by QSP-SIG.

Register now to receive early bird pricing!

C-13: *Yevgen Ryeznik* Adaptive dose finding for time-to-event outcomes with adaptive choice of patient number based on response rate

Yevgen Ryeznik (1, 2), Oleksandr Sverdlov (3), Andrew C. Hooker (2)
(1) Department of Mathematics, Uppsala University, (2) Department of Pharmaceutical Biosciences, Uppsala University, (3) EMD Serono

Objectives: Many clinical trials use time-to-event (TTE) outcomes as primary measures of efficacy or safety. D-optimal and adaptive D-optimal designs for dose finding clinical trials with censored TTE outcomes were developed in [1] as efficient designs in order to determine dose-response relationship. It was shown that in presence of censoring TTE observations [2] these designs are more efficient than classical uniform (balanced) design. However, the accuracy of the dose-response estimation depends on how much data is censored, i.e. more patients are needed if the response rate is low. In this work we present a stopping criterion to resolve this issue.

Methods: We consider an accelerated failure time (AFT) model [3] assuming a quadratic dose-response model for log-transformed TTE outcomes with a Weibull distribution that are subject to right censoring with a fixed or random censoring time. For implementing optimal designs in practice a multi-stage adaptive design is applied. We propose a maximum allowed value of the relative standard error (RSE) for all parameter estimates as a stopping criterion for the study. Patients are randomized in cohorts, and after each cohort responds we estimate model parameters and check the RSE of estimated parameters. If they are less than some predefined value, we stop the randomization. Otherwise, we randomize a new, optimized, cohort.

Results: The proposed stopping criteria allows the adaptive choice of number of patients involved in a clinical trial. For high response rates we need fewer patients, while the number increases for a low response rate. The number of patients needed with this adaptive design is much less than required with a standard uniform design. In fact, even with a very large patient numbers, the standard uniform design provides biased estimations of the model parameters. The adaptive designs provide the same variability of estimated parameters as D-optimal (non-adaptive) designs if the number of randomized patients is 25% larger than the corresponding number for the D-optimal design (assuming that the D-optimal design has perfect information about model parameters BEFORE the start of the experiment, an unrealistic situation).

Conclusion: The proposed stopping criteria can improve efficiency of clinical trials with time-to-event outcomes by adapting the number of recruited patients based on response rate.

References:
[1] Ryeznik Y, Hooker AC, Sverdlov O Adaptive designs for dose finding clinical trials with time-to-event outcomes. PAGE 24 (2015) Abstr 3608 [www.page-meeting.org/?abstract=3608]
[2] Lawless JF. Statistical Models and Methods for Lifetime Data, 2nd Edition, Wiley, New York (2003).
[3] Wei LJ. The accelerated failure time model: A useful alternative to the Cox regression model in survival analysis. Statistics in Medicine 11(14-15):1871-1879 (1992).

C-14: *Sebastian Wicha* A general pharmacodynamic interaction model based on the Bliss Independence criterion

Sebastian G. Wicha, Chunli Chen, Oskar Clewe and Ulrika S.H. Simonsson
Dept. of Pharmaceutical Biosciences, Uppsala University, Sweden

Objectives: Quantification of pharmacodynamic (PD) drug interactions is challenging. When reviewing current approaches, published PD interaction models [1] display several limitations: (i) evaluation of PD interactions is performed on observed effects instead of PD parameters and are often mono-dimensional; (ii) interaction models do not collapse to established additivity criteria; (iii) interaction parameters have no quantitative meaning and (iv) some models lack the possibility to capture more than two interacting drugs. The objective of the present work was to define a general PD interaction (GPDI) model overcoming all these limitations.

Methods: The Bliss Independence (BI) additivity criterion ($E_{A,B}=E_A+E_B-E_AE_B$) was extended to quantify interactions in the GPDI model. Scaling was utilised to account for differences in Emax between drugs [2]. The interaction term was implemented as fractional change on the effect parameter (EC50 or slope or Emax) altering E_A and/or E_B in presence of the combination drug. The interactions between E_A and E_B were bi-directionally quantified by means of Emax models by INT_{AB} and INT_{BA} (maximum fractional change of the effect parameter) and $EC50_{INT,AB}$ and $EC50_{INT,BA}$ (interaction potencies). Interaction models for more than 2 drugs were also derived. Simulations and design explorations were performed in R (v 3.2.1).

Results: The GPDI model was successfully derived. For two drugs, four parameters quantified the possible interactions, but a reduced model with one interaction parameter was also derived. For INT=0, the GPDI model collapsed to BI (additivity), whereas for -1<INT0 antagonism was quantified. INT is to be interpreted as fractional change of drug potency/efficacy. Simulation studies displayed its flexibility and design explorations indicated identifiability of the GPDI model.

Conclusion: The GPDI model allows for multi-dimensional quantification of PD interactions providing interpretable interaction parameters thereby being in accordance with the BI criterion. The model has been successfully used in pre-clinical studies of the combined effect of anti-tubercular drugs in *in vitro* and animal studies [3,4] and can be applied in both concentration-effect and longitudinal modelling activities. Application of the GPDI model in other settings and therapeutic areas with high prevalence of combination therapy seems promising.

References:

[1] D.M. Jonker, S.A.G. Visser, P.H. van der Graaf, R.A. Voskuyl, M. Danhof. Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. *Pharmacol. Ther.*, 106: 1–18 (2005).
[2] S.G. Wicha, M.G. Kees, J. Kuss, C. Kloft. Pharmacodynamic and response surface analysis of linezolid or vancomycin combined with meropenem against Staphylococcus aureus. *Pharm Res*, 32: 2410–2418 (2015).
[3] O Clewe, S.G. Wicha, C. de Vogel, J.E.M de Steenwinkel, U.S.H. Simonsson. Pre-clinical susceptibility characterization and pharmacodynamic interaction assessment using the multistate tuberculosis pharmacometric model. 25th PAGE Meeting, Lisbon (2016).
[4] C. Chen, S.G. Wicha, G.J. de Knegt, J.E.M. de Steenwinkel, U.S.H. Simonsson. Assessment of pharmacodynamic interactions in the mycobacteria tuberculosis infected mouse using the multistate tuberculosis pharmacometric model. 25th PAGE Meeting, Lisbon (2016).

Acknowledgement: The research was funded by the Swedish Research Council and the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement n°115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

C-15: *Martin Fink* Improving priors for human mAb linear PK parameters by using half-lives from pre-clinical studies

Martin Fink (1), Philip J Lowe (1), Vittal Shivva (2)
(1) Novartis Pharma AG, Basel, Switzerland; (2) University of Otago, Dunedin, New Zealand

Objectives: Obtaining a good prior for the linear PK part of new monoclonal antibodies (mAb) is essential for designing first-in-man (FIM) studies but also for fitting possible non-linear target-mediated disposition observed in these studies early-on.

Methods: Non-human primate (NHP) studies and FIM studies for six mAbs were fitted with 2cmt PK models, first separately, later together using a simple pool, a model with a 3rd hierarchical random effects ($LEVEL, NM7.3+) and a model including covariates for between mAb differences. Two other mAbs with slightly nonlinear PK were included for comparison.

Results: There was good agreement between compounds for the central volume (reflecting the rapidly accessible plasma volume Vp of 2.9L for a 70kg man), but the tissue volume (Vti) and clearance (CL) differed substantially – leading to terminal half-lives ranging from 15 to 28 days (plausibly due to differences in FcRn binding, charge distribution, glucolysation, etc. – see e.g., [1,2]). Inter-compartmental flow estimates were variable but mostly with poor precision.
One of the two nonlinear compounds showed, despite similar typical parameter values, greater inter-individual variability (IIV) in Vti (47 %CV) whereas the other showed much larger CL, Vp and Vti, perhaps due to rapid binding to readily available membrane-bound receptors.
The simple pool of human studies (similar to [3]) gave larger IIV estimates (CL 32 %CV, Vti 35 %CV) than the separate fits (CL 13-26 %CV, Vti 10-36 %CV); as inter-mAb-variability was being added to the IIV. The pool using a 3rd hierarchical random effect and adding drug specific covariates gave IIV estimates close to those of the separate fits (CL 23 %CV, Vti 23 %CV).
The between-mAb differences were predictable using allometric scaling and terminal half-life estimates from NHP, which showed less than 13% difference from their respective human estimates (consistent with [4]).

Conclusions: Ignoring inter-mAb variation leads to inflated estimates of IIV. However, by using just the terminal half-life estimates from NHP data one can account for between-mAb-differences in human and thus provide non-inflated priors for the linear PK of new mAbs.

References:
[1] Suzuki et al., Importance of Neonatal FcR in Regulating the Serum Half-Life of Therapeutic Proteins Containing the Fc Domain of Human IgG1: A Comparative Study of the Affinity of Monoclonal Antibodies and Fc-Fusion Proteins to Human Neonatal FcR, J Immunol 2010.
[2] Datta-Mannan et al., The interplay of non-specific binding, target-mediated clearance and FcRn interactions on the pharmacokinetics of humanized antibodies, mAbs 2015.
[3] Davda et al., A model-based meta-analysis of monoclonal antibody pharmacokinetics to guide optimal first-in-human study design, mAbs 2014.
[4] Zhao et al., Across-Species Scaling of Monoclonal Antibody Pharmacokinetics Using a Minimal PBPK Model, Pharm Res 2015.

C-16: *David McDougall* The Impact of Model Selection for Personalised Dosing

David AJ McDougall (1,2), Jenny Martin (3), E Geoffrey Playford (4,5), Bruce Green (2)
(1) School of Pharmacy, University of Queensland, Brisbane, Australia; (2) Model Answers Pty Ltd, Brisbane, Australia; (3) School of Medicine and Population Health, University of Newcastle, New South Wales, Australia; (4) School of Medicine, University of Queensland, Brisbane, Australia; (5) Infection Management Services, Princess Alexandra Hospital, Brisbane, Australia.

Objectives: Model based personalised dosing (MBPD) is a form of individualised therapy where patient specific pharmacokinetic (PK) or pharmacodynamic parameters are estimated in real-time. Little research has been conducted to evaluate how the choice of model impacts dose recommendations. Voriconazole, a triazole antifungal with nonlinear kinetics is the motivating example used in this research. Model selection for voriconazole MPBD is potentially critical, as many different structural models are present in the literature. The aim of this work was to assess the impact of model miss-specification on dose recommendations and clinical outcomes.

Methods: Five reduced miss-specified population models were developed from a published model by removing key structural components. [1] Parameters for the reduced models were developed using the stochastic simulation and estimation functionality in PsN.[2] The dose adjustments required to reach a target concentration in 100 simulated subjects were determined using the empirical Bayes estimates. The expected plasma concentration that would have resulted from the dose recommendations was derived from the simulated PK parameters. Logistic regression models linking exposure to clinical response[3] and neurotoxicity[4] were applied to the predicted plasma concentrations to assess the probability of clinical outcomes.

Results: Removing CYP2C19 genotype as a covariate on clearance resulted in similar dose recommendations to the required doses with minimal impact on the plasma concentrations achieved and percentage of subjects within the therapeutic range. The models with only linear clearance performed poorly, recommending large doses that would have resulted in toxic exposure. The probability of clinical success was similar for all the models. The probability of neurotoxicity was lowest when the model contained non-linear clearance. The median probability of neurotoxicity increased 4-8 fold when a model with linear clearance was used.

Conclusion: Structurally miss-specified clearance had a large impact on plasma concentrations and the likelihood of toxicity. This is relevant for voriconazole as several published models have only linear clearance.[5-9] Removing genotype was of little importance given the probability of clinical response and neurotoxicity was comparable. Once plasma concentrations become available, the benefit of genotype in MBPD is of little benefit.

References

[1] McDougall DA, Martin J, Playford EG, et al. Determination of a suitable voriconazole pharmacokinetic model for personalised dosing. J Pharmacokinet Pharmacodyn 2015
[2] Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Computer methods and programs in biomedicine 2005;79(3):241-57.
[3] Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother 2011;55(10):4782-8.

[4] Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis 2012;55(3):381-90.
[5] Wang T, Chen S, Sun J, et al. Identification of factors influencing the pharmacokinetics of voriconazole and the optimization of dosage regimens based on Monte Carlo simulation in patients with invasive fungal infections. J Antimicrob Chemother 2013.
[6] Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis 2012;55(3):381-90.
[7] Han K, Capitano B, Bies R, et al. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. Antimicrob Agents Chemother 2010;54(10):4424-31
[8] Nomura K, Fujimoto Y, Kanbayashi Y, et al. Pharmacokinetic-pharmacodynamic analysis of voriconazole in Japanese patients with hematological malignancies. Eur J Clin Microbiol Infect Dis 2008;27(11):1141-3.
[9] Han K, Bies R, Johnson H, et al. Population pharmacokinetic evaluation with external validation and Bayesian estimator of voriconazole in liver transplant recipients. Clin Pharmacokinet 2011;50(3):201-14.

D-01: *Lutz Harnisch* Modelling and simulation of neurological endpoints (modified Rankin Scale [mRS] and National Institute of Health Stroke Scale [NIHSS]) to aid clinical trial design in intracerebral hemorrhage (ICH)

Rik Schoemaker(1), Satyaprakash Nayak(2), William S. Denney(2), E. Niclas Jonsson(3), Mats O. Karlsson(3), Lutz O. Harnisch (2), on behalf of the VISTA-ICH Collaborators
(1) Occams, (2) Pfizer Inc., (3) Pharmetheus AB

Objective: To develop a modeling and simulation framework for longitudinally observed mRS and NIHSS scores in patients with intracerebral hemorrhage (ICH) based on the placebo subject-level data from the VISTA-ICH [1] database.

Methods: mRS and NIHSS were modeled using categorical and continuous data models, respectively, where an underlying Emax time-profile allowed for an individual improvement or deterioration over time. The two endpoint scales were combined into a single model to estimate the correlation between model components and improve the model power. Covariate effects were implemented for the models by estimating the effect of ICH hematoma volume on mRS and NIHSS at baseline, and by estimating the effect of change in ICH hematoma volume (a future treatment target) on the fraction of patients improving. Covariate effects were simulated to quantify impact on outcomes for both scales at day 90 and to quantify the effect of reducing the hematoma volume increase on those outcomes. Trial simulations allowed power estimates for various longitudinal models, different sampling schedules, and different effect sizes using the Parametric Power Estimation approach [2] and contrasting it to a traditional logistic regression approach.

Results: Both the mRS-alone model and the combined mRS/NIHSS model provided an adequate description of the evolution of mRS scores over time. The combined model established two populations, improvers or deteriorators in the VISTA-ICH placebo data. The parameters for the base model component, Emax and fraction improvers were found to be highly correlated across these two scales. Simulations showed that for VISTA placebo data, small hematoma baseline volumes were associated with a favorable outcome, but substantial reductions in hematoma volume increase would be required to increase the probability of a favorable outcome.

Conclusion: The model predicted that a large reduction in hematoma volume increase would likely have a substantial impact on mRS outcome scores, providing us with an estimate for a desired target effect size. Since mRS and NIHSS profiles are highly correlated NIHSS used in conjunction with mRS will improve the prediction precision of the clinical outcome and therefore lead to much smaller trial sizes. The effect of a combined longitudinal endpoint could be quantified through power calculations to guide the design of a future trial.

References:
[1] - VISTA: The Virtual International Stroke Trials Archive at http://www.vista.gla.ac.uk/
[2] - Ueckert S, Karlsson MO, Hooker AC, Accelerating Monte-Carlo Power Studies through Parametric Power Estimation, PAGE 23 (2014) Abstr 3263 [http://www.page-meeting.org/?abstract=3263]

D-02: *Oliver Sander* Model-based development of the secukinumab dosing regimen for the treatment of moderate-to-severe chronic plaque psoriasis

Oliver Sander, Achim Guettner, Charis Papavassilis, Michael Looby
Novartis Pharmaceuticals, Basel Switzerland

Objectives: In order to identify optimized dosing regimens for phase 3, this model-based analysis integrated data from several phase 2 studies that were collected under different conditions (i.e., different routes of administration, doses and dosing regimens, and study duration). The analysis was subsequently used to justify the selected regimens in the phase 3 study protocols, and at health authority meetings (end-of-phase-2 and advisory committee meeting after phase 3).

Methods: Accompanying the phase 2 program, a PKPD model was built in serveral iterations. When a new study read out, prior predictions of the read-out were checked against the new results and the model was subsequently refined and updated. A two-compartment PK model with zero-order (to account for IV adminstration) and first-order absorption (to account for SC administration) was fit to concentration data. Turnover models were fit to the continuous efficacy data (PASI score). Model assessment was performed using standard goodness of fit diagnostics, visual predictive checks, and external validation by prosectively predicting outcomes of the next read-outs.

Results: PK was described by a two compartment disposition model. PD was described by a turnover model with stimulatory effect on the decrease of disease activity (Kout), driven by a sigmoidal Emax model as a function of drug concentration. This model was considered predictive, as it captured the main trends across doses, dosing regimens and routes well. Based on this model, regimens were evaluated and two SC regimens were selected to move into phase 3: 150mg and 300mg given at weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. These two regimens were predicted to improve response over the subcutaneous regimens used in phase 2 and other available treatments.

Conclusions: Through sequential integration of phase 2 data in model-based analyses, it was possible to recommend dosing regimens for phase 3 which had not been previously tested.The phase 3 studies confirmed the efficacy and safety of these new regimens, leading to regulatory approval of a product with optimized efficacy. With complex development programs, aimed at answering a set of complex questions – e.g. different routes of administration, a large space of possible regimens, comparison to competitors, short- and long-term effects – model-based integration of “the puzzle pieces” offers a rational and quantitative approach to support decision making.

References:
[1] Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm. (1993) 21(4):457-78.
[2] Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai TF, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C; ERASURE Study Group; FIXTURE Study Group. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. (2014) 371(4):326-38.

D-03: *Rasmus Vestergaard Juul* Repeated time to event modelling of opioid consumption in postoperative pain

Rasmus Vestergaard Juul (1), Joakim Nyberg (2), Mads Kreilgaard (1), Lona Louring Christrup (1), Ulrika SH Simonsson (2), Trine Meldgaard Lund (1)
1: Department of Drug Design and Pharmacology, University of Copenhagen, Denmark, 2: Department of Pharmaceutical Biosciences, Uppsala, Sweden

Objectives: Postoperative pain trials often rely on patient controlled analgesic consumption as an endpoint of analgesic effect despite great concerns on traditional approaches to data analysis [1,2]. Pain intensity and consumption of rescue medication follows recurrent patterns of pain progression, pain events, patient controlled rescue medication, exposure to rescue analgesics and pain relief in time [3]. How to meaningfully analyse patient controlled analgesic consumption remain an obstacle to advances in postoperative pain management [4]. This work aimed to explore Repeated Time-to-Event (RTTE) modelling for analysis of consecutive analgesic consumption.

Methods: Data of patient requested morphine with three formulations and a range of doses (2.5-30 mg) in the postoperative pain period until 96 h or loss to follow-up after hip fracture surgery was obtained [5,6]. RTTE modelling was used to describe the timing of morphine consumption events [5]. A PK-PD model for the effects of morphine on the probability of subsequent morphine consumption was developed [6]. A RTTE simulation approach was developed of adaptive dosing in the presence of time-varying covariates [6]. A simulation study was performed to compare RTTE modelling to traditional analysis approaches; t-test, Mann-Whitney test and time-to-event modelling [7].

Results: A Gompertz distribution RTTE model described the data well. The probability of analgesic events decreased in time, was reduced to 50% after 3.3 days after surgery and was significantly lower (32%) during night compared to day. For the first time, the PK-PD relationship between morphine and the probability of subsequent morphine consumption could be determined (EC50 = 1.9 ng/mL, Emax = 78% reduction). A hypothetical adjuvant drug X was simulated to have 37% morphine sparing effect. In a 24 h trial allowing morphine as rescue medication, a sample size of 50 patients was required to detect a significant reduction in morphine consumption with at least 80% power with RTTE modeling. In comparison the required sample size was 200 for Mann-Whitney, 180 for t-test and 76 for time-to-event modelling.

Conclusion: This study demonstrates the value of RTTE modelling for the study of analgesic consumption in postoperative pain. RTTE modelling allows future studies to use opioid consumption data to study analgesic interventions accounting for time-varying factors such as pain intensity, analgesic exposure and pain relief [8].

References

1. Kissin I (2009) Patient-controlled-analgesia analgesimetry and its problems. Anesthesia and analgesia 108 (6):1945-1949.
2. Moore RA, Mhuircheartaigh RJ, Derry S, McQuay HJ (2011) Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. European Journal of Anaesthensiology 28 (6):427-432.
3. Sheiner LB (1994) A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. Clinical pharmacology and therapeutics 56 (3):309-322
4. US Food Drug Administration (2014) Guidance for industry analgesic indications: developing drug and

biological products. Available from:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf [accessed 2015 Mar 12].
5. Juul RV, Rasmussen S, Kreilgaard M, Christrup LL, Simonsson USH, Lund TM (2015) Repeated time-to-event analysis of consecutive analgesic events in postoperative pain. Anesthesiology 123 (12):1411-1419
6. Juul RV, Nyberg J, Lund TM, Rasmussen S, Kreilgaard M, Christrup LL, Simonsson USH (2016; DOI: 10.1007/s11095-015-1853-5) A Pharmacokinetic-Pharmacodynamic Model of Morphine Exposure and Subsequent Morphine Consumption in Postoperative Pain. Pharmaceutical research.
7. Juul RV, Nyberg J, Kreilgaard M, Christrup LL, Simonsson USH, Lund TM (2016) Optimal analysis and design of trials investigating analgesic consumption in postoperative pain. Submitted
8. Houle TT (2015) An Innovative Analysis of Analgesic Consumption in the Postoperative Period. Anesthesiology 123 (6):1227-1228

D-04: *Thu Thuy Nguyen* Limited sampling strategy for a population pharmacokinetic modelling of cocktail of phenotyping drugs

Thu Thuy Nguyen (1,2), Henri Bénech (3), Marcel Delaforge (3), France Mentré (1), Natacha Lenuzza (2)
(1) IAME-UMR 1137, INSERM and University Paris Diderot, Paris, France; (2) CEA, LIST, LADIS, Gif-sur-Yvette, France; (3) CEA, DSV, iBiTecS, Gif-sur-Yvette, France

Objectives: Cocktail approach using a combination of probes to phenotype several cytochromes P450 and transporters, is of high interest in anticipating drug-drug interactions and personalized medicine [1]. Phenotyping indexes (PI) which are obtained from the area under the concentration-time curves, can be derived from a few samples using nonlinear mixed effect models (NLMEM) and maximum a posteriori estimation. We aimed to 1) propose a limited sampling strategy, allowing correct estimation of PI for several probes while providing as much flexibility as possible in sampling timing; 2) illustrate this strategy for two drugs often used in phenotyping tests: midazolam (probe for CYP3A) and digoxin (P-glycoprotein).

Methods: Data of a previous study with ten healthy volunteers [1] were analyzed to develop population parent/metabolite models for several drugs. In order to optimize joint design for a cocktail, we proposed to use the compound D-optimality [2] by maximizing a weighted sum of log determinants of the expected population Fisher information matrix (FIM) [3] for these models. Sampling windows were computed around the optimal fixed times, based on recursive random sampling and Monte-Carlo simulation [4,5], satisfying an expected joint loss of efficiency below 10% for each molecule. We illustrated this strategy to find a sparse and flexible design common to three compounds: midazolam, its metabolite 1-OH-midazolam and digoxin. The obtained design was evaluated by clinical trial simulations for estimation of population and individual PI.

Results: A two-compartment model (first order absorption, linear elimination) adequately fitted the concentrations of digoxin while a joint two-compartment-parent/one-compartment-metabolite model was found for midazolam and 1-OH-midazolam. The common design ξ was composed of six samples (0.25, 1, 2.5, 5, 12, 48h post-administration) instead of nine samples if optimizing separately design for each drug, giving predicted relative standard errors below 20% for both PI. The window design achieved an efficiency above 90% relative to ξ for population analysis of each drug and showed good performance for estimation of individual PI.

Conclusions: By combining NLMEM, compound design and sampling windows based on FIM, we were able to determine sparse and flexible samples allowing correct estimation of PI for three compounds [6]. This approach can be used to efficiently design studies with cocktails including more drugs.

References:

[1] Lenuzza N, Duval X, Nicolas G, Thévenot E, Job S, Videau O, Narjoz C, Loriot MA, Beaune P, Becquemont L, Mentré F, Funck-Brentano C, Alavoine L, Arnaud P, Delaforge M, Bénech H. Safety and pharmacokinetics of the CIME combination of drugs and their metabolites after a single oral dosing in healthy volunteers. Eur J Drug Metab Pharmacokinet 2014 [Epub ahead of print].
[2] Atkinson AC. DT-optimum designs for model discrimination and parameter estimation. J. Stat. Plan. Inference 2008; 138(1): 56–64.
[3] Mentré F, Mallet A, Baccar D. Optimal design in random-effects regression models. Biometrika 1997; 84(2): 429–442.
[4] Foo LK, McGree J, Duffull S. A general method to determine sampling windows for nonlinear mixed

effects models with an application to population pharmacokinetic studies. Pharm Stat 2012; 11(4): 325–333.
[5] Ogungbenro K, Aarons L. An effective approach for obtaining optimal sampling windows for population pharmacokinetic experiments. J Biopharm Stat 2009; 19(1): 174–189.
[6] Nguyen TT, Bénech H, Delaforge M, Lenuzza N. Design optimisation for pharmacokinetic modeling of a cocktail of phenotyping drugs. Pharm Stat 2015 [Epub ahead of print].

D-07: *Sylvie Retout* How disease modeling and model-based meta-analyses contributed to understanding the path forward after dose discontinuation of a Phase III study in Alzheimer's disease

Sylvie Retout (1), Ronald Gieschke (1), Cornelia Weber (1), Jean-Eric Charoin (1), Dietmar Volz (2), Robert Lasser (2), Carsten Hofmann (1), Nicolas Frey (1)
(1) Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland, (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: SCarlet RoAD (SR) was designed as a pivotal Phase 3 study to evaluate the effect of monthly subcutaneous doses of 105 and 225 mg anti-amyloid compound gantenerumab (GAN) in prodromal Alzheimer's disease (AD) patients. Dosing was discontinued based on results of a pre-planned futility analysis of the clinical endpoints (N=312, 2 years completers). At the same time, Phase 1b results of aducanumab (ADU) [1], a very similar compound, became available, exploring much higher doses and suggesting that GAN was under-dosed. Leveraging a previously developed disease progression model [2] and available ADU data, we investigated the reasons of the futility results and uncovered a way forward.

Methods: The AD progression model was used to split the SR patients into SLOW progressors (SP) or FAST progressors (FP) based on 3 covariates at baseline (FAQ, CDR-SB and hippocampal volume). The GAN effect on AD scales time courses (ADAS-Cog13, CDR-SB, MMSE and CANTAB), was graphically investigated per category of SP/FP. Relationships between drug concentration and brain amyloid plaque removal measured by PET and between drug concentration and early amyloid related imaging abnormality vascular edema (ARIA-E) were modeled, as a GAN and ADU data meta-analysis. Both models are detailed in the 2016 PAGE abstracts [4] and [5].

Results: The lack of significant drug effect detection in SR could be explained by a relatively small proportion of FP (only one third at study entry), and doses that were too low. A clear exposure–ADAS-Cog13 relationship was observed among FP with a median decrease of 3 points at 2 years in the highest exposure group compared to placebo. Similar exposure trends were observed for MMSE and CANTAB. No exposure trend was observed among SP. Both PET and ARIA-E models described internal and external data well. Using simulations, up-titration dosing regimens were found to balance ARIA-E events and plaque removal, increasing the Ph3 success likelihood.

Conclusions: Quantitative clinical pharmacology tools, including disease modeling and exposure-response meta-analyses, shed positive lights on the GAN Phase 3 program and guided up-titration regimens using higher doses for a higher chance of success. Those GAN dosing regimens are currently being investigated in ongoing studies.

References:

[1] Sevigny, J et al. 67th Annual Meeting of the American Academy of Neurology, Washington DC, US (2015)
[2] Delor, I et al. CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e78
[3] Hutmacher, M et al. 7th American Conference on Pharmacometrics, Fort Lauderdale, US (2013)
[4] Frey, N et al. Abstr PAGE 25, Lisbon, Portugal (2016) [5] Gieschke, R et al. Abstr PAGE 25, Lisbon, Portugal (2016)

D-08: *Marc Vandemeulebroecke* A longitudinal Item Response Theory model to characterize cognition over time in elderly subjects

Marc Vandemeulebroecke, Johanna Mielke, Peter Quarg, Tillmann Krahnke, Björn Bornkamp, Andreas Monsch
Novartis Pharma AG; Memory Clinic Basel

Objectives: The goals of this work were to investigate which cognitive domains carry most information on earliest signs of cognitive decline in the elderly, to characterize the subjects' cognitive trajectory over time and to understand which subject characteristics impact this trajectory. This is relevant for better understanding whom to treat and what to measure in early intervention trials in slowly progressing neurodegenerative diseases such as Alzheimer's disease (AD).

Methods: A longitudinal Item Response Theory (IRT) model was developed for cognitive data from the BASEL study, in which 1750 mostly healthy elderly subjects were observed over up to 14 years per subject. The model extends an earlier cross-sectional model [1] (which was inspired by [2]) into a fully longitudinal IRT model, in which the multifaceted nature of the response and its longitudinal trajectory are modeled jointly. It was implemented in a Bayesian framework with noninformative priors, using WinBUGS, JAGS and STAN.

Results: 'CVLT-Word List Learning' and 'CERAD-Word List Learning' as well as 'CVLT-Word List Long Delay Free Recall' and 'CERAD-Word List Delayed Recall' carried most information in the BASEL sample (15.5%, 13.1%, 10.3% and 8.8%, respectively, of the total amount of information). The Mini Mental Status Examination (MMSE) and word list recognition tasks were informative only in the range of low cognitive abilities. Greater age at baseline, positive APOE4 carrier status, and less years of education were significantly associated with a faster cognitive decline. WinBugs, JAGS and STAN provided virtually identical results. JAGS provided the best compromise between efficiency and practicality.

Conclusions: Fully longitudinal IRT modeling, as applied here in a mostly healthy elderly population, is a suitable method to capture the multifaceted nature of cognition and its longitudinal trajectory jointly. It is computationally more intensive than cross-sectional IRT models (such as [1] and [2]), but it allows the estimation of the IRT parameters based on all data. It would be of interest to apply this method also to a cohort with prodromal or mild AD.

References:
[1] Vandemeulebroecke M, Mielke J, Krahnke T, Monsch AU (2014). Identifying neuropsychological domains with high information on early signs of cognitive decline. PAGE conference
[2] Ueckert S, Plan EL, Ito K, Karlsson MO, Corrigan B, Hooker AC (2013). Benefits of an Item Response Theory Based Analysis of ADAS-Cog Assessments. American Conference on Pharmacometrics

D-09: *Simon Buatois* Utilizing the items from the MDS-UPDRS score to increase drug effect detection power in de novo idiopathic Parkinson's disease patients

Simon Buatois (1,2), Sylvie Retout (1), Nicolas Frey (1), Sebastian Ueckert (2,3)
(1) Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland; (2) IAME, UMR 1137, INSERM, F-75018 Paris, France, Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France; (3) Pharmetheus AB, Uppsala, Sweden

Objectives: In Parkinson's disease (PD) clinical trials, total score of clinical rating scales, such as MDS-UPDRS [1], is traditionally used to assess the treatment efficacy [2]. However, the high number of failed clinical trials has led to challenge its use as a clinical end point [3-5]. As a result, pharmaceutical companies are increasingly moving to an analysis of subsets of the scale. These subsets are often selected per items family (e.g. motor items), and do not take the sensitivity of each item to a drug effect into account, leading to a potential loss of power. The objectives of this work was first, to construct a subset of the MDS-UPDRS which maximizes the power to detect a drug effect acting on the disease progression (DEDP) in de novo PD patients, and secondly, to compare those results with the ones obtained with an IRT-based analysis.

Methods: An updated version of the IRT model [6], integrating three different pathophysiological processes with different progression rate, was built to analyze the data from the Parkinson's Progression Marker Initiative database [7]. Based on this model, clinical trial simulations were performed in de novo PD patients with a balanced, placebo versus disease modifying agent, parallel-arm study design. The power to detect a DEDP was computed under several scenarios (with different study durations and drug effects), through the use of three methods: a summary score based analysis i) of the total number of simulated items ii) of the optimal set of items (determined using a greedy algorithm [8]) and iii) an IRT based analysis.

Results: A three latent variables IRT based modeling allowed an adequate description of the data at both item and total score level taking into account the difficulty and the power of discrimination of each item. Compare to the classical analysis, the power to detect a DEDP was increased when using an optimal set of items (e.g. up to 20% increase for a 50% DEDP). However, it requires an accurate approximation of drug effect prior to the analysis, as the optimal set varied between scenarios. The IRT based analysis increased further the power without the need of items selection.

Conclusions: Selection of the most sensitive items of the MDS-UPDRS score can be used to increase the power of a summary score analysis. Nevertheless, an IRT analysis based on all collected data items increase further the power to detect a DEDP without any need of an apriori assumption on its magnitude and is recommended.

References:
[1] C G Goetz et al, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale, Movement Disorders, 2007 Jan, 22(1):41-7
[2] Ramaker, C., Marinus, J., Stiggelbout, A. M., & Hilten, B. J. (2002). Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Movement Disorders Mov Disord., 17(5), 867-876.
[3] Kalia L, Lang A. Parkinson's disease. The Lancet. 2015;386(9996):896-912.
[4] Louis E, Tang M, Cote L, Alfaro B, Mejia H, Marder K. Progression of Parkinsonian Signs in Parkinson Disease. Arch Neurol. 1999;56(3):334.
[5] Vu T, Nutt J, Holford N. Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. British Journal of Clinical Pharmacology. 2012;74(2):267-283.

[6] Buatois S, Retout S, Gieschke R, Ueckert S, Frey N. Using Item response theory to yield information from the MDS-UPDRS items in Parkinson's disease clinical trials. http://www.page-meeting.org/?abstract=3417
[7] PPMI: Parkinson's Progression marker initiative www.ppmi-info.org/data
[8] Cormen T. Introduction to algorithms. Cambridge, Mass.: MIT Press; 2009.

I-01: *Thomas Dumortier* Using extrapolation to support a pediatric investigational plan: an application in liver transplantation development

Thomas Dumortier, Ovidiu Chiparus, Martin Fink
Novartis Pharmacometric department

Objectives: Support a pediatric investigational plan (PIP) for everolimus® in liver transplantation (Tx) in 2015, using a model based approach.

Methods: The paediatric study included 22 patients treated with everolimus (EVR) and tacrolimus (TAC) for a 12-months period ('analysis period'), starting from 1.5 to 6 months after Tx. The analysis of this study was supported by an extrapolation from an adult phase 3 study, using a PKPD approach. In that study, 740 patients were treated with TAC and EVR or TAC alone. The effect of drug concentration on the hazard of efficacy event (acute rejection, graft loss, death) was estimated from the adult data by means of a time-to-event model, similarly as done in [1]. In this model, the concentration was predicted from population PK models. The extrapolation concept is that this concentration-event relationship also holds in children. Under this assumption, the efficacy of patients treated similarly to those in the paediatric study could be predicted. This concept was validated using internal and external methods.

Results: The final model developed from the adult data includes a concentration-response relationship for TAC and a treatment effect for EVR. The validation of the extrapolation procedure was based on very high probabilities (predicted from the final model) to observe the actual results of the paediatric study (no events among the 22 patients during the analysis period) and the results of a published paediatric study [2]. Therefore the final adult model could be used to calculate with high precision the probability for a paediatric patient to experience events during the analysis period, as equal to 0.023 (95% CI = [0.012-0.039]).

Conclusions: In indications such as transplantation, enrolling a sufficient numbers of patients is challenging. In this context, leveraging relevant available data in adults may facilitate the evaluation of paediatric treatment effectiveness. Extrapolation using a PKPD approach supported evidence from the pediatric study that efficacy was the same or better in children than adults.

References:
[1] Dumortier T. Estimating the contribution of everolimus to immunosuppressive efficacy when combined with tacrolimus in liver transplantation: a model-based approach. Clin. Pharmacol. Ther. (2015) Apr;97(4):411-8
[2] Kelly D. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation. Lancet (2004) Sep 18-24;364(9439):1054-61

I-02: *Mike Dunlavey* A new language for complex ODE models

Michael Dunlavey(1), Shuhua Hu(1), Robert Leary(1)
(1) Certara/Pharsight Corp.

Objectives: Complex models such as HIV/HCV/HBV, and possibly some diabetes models as in the DDMoRe model repository[1], when represented as differential equations, tend to dramatically increase in length and width as modifications, such as mutations or treatments are made, even though the modifications are easily foreseen. The differential equations tend to have many repeated terms that are the same except for a sign, or almost the same as others. At the same time, the functional purpose of each term is often hard to discern. This weighs against the verifiability and modifiability of such models. The objective is to find a surface representation of such models that reduces these problems.

Methods: A prototype language is given, designed to allow easy extension of a model to include additional treatments and compartments. It allows easy extension along multiple dimensions, and it allows separation of independent model sections such as elimination, infection, activation, etc. The model specifies "dimensions", where a typical dimension could be active vs. resting, applied to cells of different types. It specifies "states" representing compartments, but they can be vectors indexed by one or more dimensions. It specifies "parameters" which can be vectors indexed by one or more dimensions. It specifies various types of flows, such as 0th-order, 1st-order, and 2nd-order. These flows can contain "i" and/or "j" in a state or parameter index. Acting as universal quantifiers, they are applied across multiple states or parameters. For example "decayrate T(i,j) del(i)" can indicate that T cells of all activities and infection states decay at the rate for the corresponding activity. If the character "*" appears in a state or parameter index, it indicates summation. For example if "T(active,*)" appears, it indicates the sum of active T cells over all infection states. The term "V(*)-V(noninf)" can represent the sum of the infective virus over all mutations (total minus noninfective virus).

Results: An HIV model given in Banks, et al [2] is encoded in the language. Then the model is modified to include a mutation, following Hu[3], and shown to simulate appropriately. The modification of the model is shown to require minimal ammendment to the original model statement.

Conclusions: A language is demonstrated that shows, in the context of an HIV model, that modifications such as addition of a virus mutation can be made with minimal coding effort and high verifiability.

References:
[1] DDMoRe Model Repository, http://repository.ddmore.eu/models
[2] Banks, H.T., Hu, S., Thompson, W.C. Modeling and inverse problems in the presence of uncertainty, CRC Press, 2014
[3] Hu, S., personal communication

I-03: *Sulav Duwal* Top-down and Bottom-Up modelling approaches in Systems Pharmacology: Understanding clinical efficacy of NRTIs against HIV-1

Sulav Duwal, Max von Kleist
Systems Pharmacology & Disease Control, Dep. of Mathematics and Computer Science, Freie University Berlin, Germany

Objectives: Systems Pharmacology aims to understand clinical mechanisms of action (MOA) of drugs to enable optimal therapy. This requires to understand how *in vitro* testable insights translate into clinical efficacy. Two modelling approaches are used, each on its own insufficient: In a top-down approach, a minimal PK-PD model is fitted to available *clinical* data, usually enabling limited mechanistic understanding and scalability. A bottom-up approach builds on mechanistic insights derived from *in vitro* experiments, but may not be representative for the clinical situation. However, a valid bottom-up approach may allow to explore untested clinical scenarios.

We focused on nucleoside reverse transcriptase inhibitors (NRTIs) used in HIV-1 treatment. NRTIs are administered as prodrugs which, after intracellular phosphorylation, exert their effect by competitively inhibiting reverse transcription of the viral genome. Our objective was to assess the validity of previously developed MOA model [1] for NRTIs using a top-down approach.

Methods: We employ bottom-up and top-down approaches concomitantly and predict the clinical potency (IC_{50} values for inhibition of target cell infection) of lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF) [3]. In the top-down approach, we established the link between the plasma prodrug PK and the intracellular NRTI-triphosphates using various parameter estimation techniques and subsequently coupled this composite PK model to viral kinetics [2] to estimate the IC_{50}. In the bottom-up approach inhibition of reverse transcriptase-mediated viral DNA polymerisation by the intracellular NRTI-triphosphates is mechanistically modelled [1]. By using disparate datasets to parameterize the respective approaches, we were able to assess the clinical predictive power of the bottom-up approach.

Results: For all NRTIs, the final model consisted of a 2-compartment model with first order absorption with saturable uptake & anabolism. Estimated IC_{50}s (0.17,1.02 and 0.74µM for TDF, FTC and 3TC) from the top-down approach showed good agreement with MOA derived IC_{50}s (0.1,0.82 and 1.72µM). We noted that the top-down IC_{50}s are highly sensitive to the intracellular PK data.

Conclusions: Validating MOA models by top down approaches is an involved, yet rewarding step in Systems Pharmacology. In our case, we were able to translate *in vitro* parameters into measure of clinical efficacy allowing us to benchmark treatment protocols prior to human trials.

References:
[1] von Kleist M, Metzner P, Marquet R and Schütte C (2012) PLoS Comp. Biol. 8: e1002359
[2] von Kleist M, Menz S and Huisinga W (2010) PLoS Comput. Biol. 6: e1000720
[3] Duwal S, von Kleist M (2016) European Journal of Pharmaceutical Sciences doi:10.1016/j.ejps.2016.01.016

I-04: *Lisa Ehmann* Pharmacokinetics of meropenem in critically ill patients with varying renal function

Ehmann L. (1,2)*, Zoller M. (3)*, Minichmayr I.K. (1,2), Scharf C. (3), Frey L. (3), Vogeser M. (4), Huisinga W. (5), Zander J. (4)**, Kloft C. (1)**

*(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) and Graduate Research Training program PharMetrX, Germany, (3) Dept. of Anaesthesiology, Hospital of the Ludwig-Maximilians-University of Munich, Germany, (4) Institute of Laboratory Medicine, Hospital of the Ludwig-Maximilians-University of Munich, Germany, (5) Institute of Mathematics, Universitaet Potsdam, Germany, * These authors contributed equally to this work, ** Shared senior authorship*

Objectives: Meropenem (MER) is a carbapenem antibiotic frequently used to treat severe infections in critically ill patients, e.g. caused by *Pseudomonas aeruginosa* [1]. In those patients an early initiation of appropriate antibiotic therapy is crucial [2]. MER is primarily excreted renally and its activity is considered to correlate with the time that concentrations are above the MIC ($T_{>MIC}$) [3]. The objective of the present work was to analyse standard dosing of MER in critically ill patients with varying renal function regarding pharmacokinetic/pharmacodynamic (PK/PD) target attainment.

Methods: MER serum concentrations (n_{total}=1424) and creatinine clearance (CLCR, estimated according to Cockcroft-Gault [4]) were obtained over 4 days in 41 critically ill patients treated with standard doses of MER as intravenous 30-min infusions every 8 h. A population PK model was developed in NONMEM 7.3 and used to simulate 1000 PK profiles for varying CLCR values (15-130 mL/min) for the first day of treatment. The probability to attain 40%$T_{>MIC}$ (=bactericidal target) was calculated for the MIC distribution of *Pseudomonas aeruginosa* (0.008-256 mg/L) [3,5]. A probability of target attainment of ≥90% was considered successful treatment.

Results: A two-compartment model adequately described MER PK in the critically ill population (CL: 8.66 L/h, Q: 30.0 L/h, V_c: 8.48 L, V_p: 17.6 L). Interindividual variability (IIV) was implemented on CL, V_c and V_p, and CLCR was found to be a significant and clinically relevant covariate on CL, explaining ~1/4 of IIV on CL. If infected with susceptible isolates (MIC ≤2 mg/L), the PK/PD target was attained for all patients - irrespective of their renal function. For the I/R breakpoint (MIC 8 mg/L) only patients with severe renal insufficiency reliably reached the target; for resistant isolates (MIC >8 mg/L), none of the investigated patients attained the target.

Conclusions: A population PK model was successfully developed to describe concentration-time profiles of MER in a critically ill population. Highest IIV was found on CL, one fourth could be explained by renal function. Standard dosing of MER resulted in adequate MER concentrations given susceptible *Pseudomonas aeruginosa* isolates. For intermediate isolates, dose adjustment seems to be required dependent on the renal function of the patient. Next, additional covariate types will be analysed to further explain the high PK variability in this vulnerable patient population.

References:

[1] GG Zhanel, R Wiebe: Comparative review of the carbapenems. Drugs 67: 1027-1052 (2007)
[2] C McKenzie: Antibiotic dosing in critical illness. J Antimicrob Chemother 66: ii25-ii31 (2011)
[3] DP Nicolau: Pharmacokinetic and Pharmacodynamic Properties of Meropenem. Clin Infect Dis 47: 32-40 (2008)
[4] DW Cockcroft, MH Gault: Prediction of creatinine clearance from serum creatinine. Nephron 16: 31-41

(1976)
[5] www.eucast.org (date of access: 18 February 2016)

I-05: *Miro Eigenmann* PBPK modeling approach to study the impact of lymph flow on the biodistribution of therapeutic antibodies

Miro Eigenmann, Ken Wang and Ludivine Fronton
Roche Pharma Research and Early Development, Pharmaceutical Sciences Roche Innovation Centre Basel, Hoffmann-La Roche Ltd., Basel

Objectives: Tissue specific blood flows (Qtis) and lymph flows (Ltis) play a major role for tissue distribution of therapeutic antibodies and are key parameters in physiologically-based pharmacokinetic (PBPK) models (1). Ltis values are currently empirically fixed as percentage of Qtis (2 or 4% for visceral or non-visceral organs) (2-4). Based on a simplified PBPK model (5),we (i) characterize the impact of Ltis on pharmacokinetics of monoclonal antibodies (mAbs); (ii) propose a range of probable Ltis values to be used in PBPK models.

Methods: Changes on mAb PK profiles caused by Ltis alterations were investigated by a sensitivity analysis in MATLAB R2013b. The extend of PK alteration was determined (i) qualitatively by visual inspection of 3D plots of altered Ltis values, time and plasma and tissue mAb concentrations; (ii) quantitatively with a gradient based scoring system.
To define a probable range for Ltis values a log-likelihood profiling (LLP) was conducted in Monolix 4.3.3 based on the PBPK model. Ltis values were sequentially fixed and altered and log-likelihood values derived. A log-likelihood profile and 95% CI were generated for each Ltis. Derived and currently assumed Ltis values were compared.

Results: Lowering Ltis values results in shallower PK profiles of mAbs, with lower Cmax, increased Tmax and slower removal from tissues. Altering Ltis of less perfused and big tissues (e.g skin or muscle) has major impact on the overall PK of mAbs, whereas in well perfused and smaller tissues (e.g. kidney) it has very limited overall impact. Main impact always occurs in the tissues where Ltis is altered.
The LLP defines a probable Ltis value range for muscle, skin and lung. For other tissues, e.g. kidney or gut, only a lower limit of Ltis could be derived. Overall the LLP suggests lower Ltis values as currently assumed.

Conclusions: Ltis affect several aspects of mAb PK: lower Ltis lead to lower Cmax and increased Tmax. Influence on the tissue itself is high while the impact on other organs is dampened by the interconnecting plasma compartment. This is new insight in differences and unexplained variability in PK of mAbs for e.g. patients with altered lymph flow due to immobility or inflammation. The LLP approach provides probable lymph flow values, is however limited for some tissues due to lack of early time points in PK data. The defined range of Ltis values from the LLP approach does not support current assumptions and suggests lower Ltis values.

References:
[1] Nestorov I. Whole body pharmacokinetic models. Clin Pharmacokinet. [Review]. 2003;42(10):883-908.
[2] Covell DG, Barbet J, Holton OD, Black CD, Parker RJ, Weinstein JN. Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')2, and Fab' in mice. Cancer Res. 1986 Aug;46(8):3969-78.
[3] Garg A, Balthasar JP. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. J Pharmacokinet Pharmacodyn. [Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't]. 2007 Oct;34(5):687-709.
[4] Jones HM, Gardner IB, Watson KJ. Modelling and PBPK simulation in drug discovery. Aaps J. [Comparative Study]. 2009 Mar;11(1):155-66.

[5] Fronton L, Pilari S, Huisinga W. Monoclonal antibody disposition: a simplified PBPK model and its implications for the derivation and interpretation of classical compartment models. J Pharmacokinet Pharmacodyn. [Research Support, Non-U.S. Gov't]. 2014 Apr;41(2):87-107.

I-06: *Raouf EL Cheikh* A New Protocol for the Administration of Etoposide–Cisplatin in Metastatic Small Cell Lung Cancer

R. El Cheikh (1), DC. Imbs (1), C. Faivre (1), J. ciccolini (1), A. Illiadis (1) and D. Barbolosi (1)
(1) Department of Pharmacokinetics, Inserm S_911 CRO2, Faculty of Pharmacy, University of Aix-Marseille, Marseille, France

Objectives: : To find new optimized temporal protocols for the combined administration of etoposide/cisplatin for small cell lung cancer (SCLC) treatment.

Methods: A PK/PD mathematical model that describes the effects of etoposide and cisplatin combination for SCLC treatment was developed. The model takes into consideration both the efficacy of drugs and their hematologic toxicity. It includes three components: the first one describes drug concentrations using compartment models, the second one is a delay differential equation system describing the hematopoietic chain and the last one describes tumor growth following a Gompertzian law. An interface model, that proved to link accurately the drugs concentrations to the perturbation of the hematopoietic chain and tumor regression, was used [1]. Model parameters were adjusted so that our simulations agree with experimental data. Through optimization techniques, the model was capable of proposing new temporal protocols that respect toxicity constraints and achieve acceptable tumor regression.

Results: Three new temporal protocols are proposed. All of them respect toxicity constraints and achieve better or similar tumor regression compared to standard protocols.
Protocol OP1 (4 cycles of 21 days): etoposide 3×80mg/m2 0h-1h, 14h-46h, 48h-72h; cisplatin 1×80mg/m2 1h-2h.

Protocol OP2 (4 cycles of 21 days): 1×72mg/m2 0h-1h, 1×96mg/m2 12h-33h, 1×68mg/m2 40h-69h, 1×52mg/m2 72h-93h, 1×112mg/m2 96h-119h; cisplatin 1×105mg/m2 1h-2h.

Protocol OP3 (intensified 6 cycles of 14 days): etoposide 1×42mg/m2 0h-1h, 1×50mg/m2 6h-30h, 1×67mg/m2 32h-72h; cisplatin 1×54mg/m2 3h-4h

Conclusions: Standard empirical approaches for optimizing drug dosing and scheduling in patients are now of limited utility as a result of the ever-growing numbers of druggable molecular targets and possible drug combinations. Consequently, mathematical modeling can play a substantial role in improving cancer treatments [2]. Mathematical models, as the one we propose here, are capable of testing *in silico* a huge number of protocols (different doses and schedules) and extract the optimized ones that meet the required toxicity-efficacy balance.

References:
[1] Meille C., Iliadis A., Barbolosi D., Frances N., and Freyer G. An interface model for dosage adjustment connects hematotoxicity to pharmacokinzetcs. J. Pharmacokinet Pharmacodyn. DOI 10.1007/s10928-008-9106-4
[2] Barbolosi D., Ciccolini J., Lacarelle B., Barlési F. and André N. Computational oncology - mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol. 2015 Nov 24. doi: 10.1038/nrclinonc.2015.204

I-07: *Yumi Emoto-Yamamoto* Development of a generic model for brain distributional pharmacokinetics and its translation to clinical data

Y Yamamoto (1), PAJ Valitalo (1), M Danhof (1), DJ van den Berg (1), R Hartman (1), W van den Brink (1), E Wong (1), D Huntjens (2), JH Proost (3), A Vermeulen (2), V Aranzana-Climent (4), C Dahyot-Fizelier (5), S Marchand (4), W Couet (4), U Rohlwink (6)

(1) Division of Pharmacology, LACDR, Leiden University, the Netherlands, (2) Quantitative Sciences, Janssen Research & Development, Belgium, (3) Division of Pharmacokinetics, Toxicology and Targeting, University of Groningen, the Netherlands, (4) Department of Medicine and Pharmacy, University of Poitiers, France, (5) Department of Anaesthesiology and Intensive Care Medicine, University Hospital Center of Poitiers, France, (6) Division of Neurosurgery, School of Child and Adolescent Health, Red Cross Children's Hospital, University of Cape Town, South Africa, (7) Department of Clinical Pharmacy, Faculty of Medicine, University of Amsterdam, the Netherlands, (8) Department of Pediatrics, Division of Intensive Care and Pediatric Surgery, Erasmus MC – Sophia Children's Hospital, the Netherlands

Objectives: To develop a generic brain distribution model using rat multilevel brain and plasma data and to translate the model to predict drug target site concentrations in human brain.

Methods: Densely sampled concentration-time profiles after administration of 9 compounds (acetaminophen, atenolol, methotrexate, morphine, paliperidone, phenytoin, quinidine, remoxipride and risperidone) to rats were collected for plasma, brain extracellular fluid (ECF), cerebrospinal fluid (CSF) from lateral ventricle (CSF_{LV}) and cisterna magna (CSF_{CM}) using microdialysis sampling. The brain distribution model structure was adapted from a previously published model [1]. A naïve pooling approach was used to fit the rat pharmacokinetic (PK) profiles. Subsequently, brain-distribution parameters were scaled to predict of human ECF and CSF data. Clinical data was available for: 1) acetaminophen plasma and CSF_{LV} concentrations obtained using external ventricular drainage in patients with traumatic brain injury (TBI), 2) acetaminophen plasma and CSF subarachnoid space (CSF_{SAS}) concentrations from patients with nerve-root compression pain, and 3) morphine plasma and ECF concentrations obtained using microdialysis from pediatric patients with TBI.

Results: The model described the PK profiles for the 9 compounds with different physicochemical properties by estimating only two parameters (clearance for drug transport at the blood-brain barrier (CL_{PL_ECF}) and brain-CSF diffusion (Q_{DIFF})). Parameters could be estimated with reasonable precision (relative standard error < 25%). CL_{PL_ECF} was different for each drug whereas Q_{DIFF} was similar for the compounds (mean±SD : 0.027 ±0.019 mL/min). The model predicted human acetaminophen CSF_{LV} and CSF_{SAS} concentrations well. The model under-predicted morphine ECF concentrations that were obtained from a patient with diffuse brain injury (normalized root-mean-square deviation (NRMSD) 48%), whereas it predicted morphine ECF concentrations adequately when the ECF data was taken from the "healthy" brain side in focally injured brain (NRMSD 25%).

Conclusions: A generic model structure was developed to capture the PK across key areas of the brain and CSF. Moreover, our model generally allowed for adequate prediction of human acetaminophen and morphine ECF and CSF concentrations. The next step will be to extend this model structure with additional physiological components to predict drug concentrations under injured/diseased brain conditions.

Reference:

[1] Westerhout J, Ploeger B, Smeets J, Danhof M, De Lange ECM. Physiologically based pharmacokinetic modeling to investigate regional brain distribution kinetics in rats. The AAPS Journal (2012)14:543-53.

I-08: *Gregory Ferl* Mechanistic model of amyloid beta (Aß) and anti-Aß mAb dynamics

Gregory Z. Ferl, Reina N. Fuji, Jasvinder Atwal, Jitendra Kanodia, Lee Honigberg, Saroja Ramanujan, Angelica L. Quartino
Genentech, Inc. 1 DNA Way, South San Francisco, CA, USA.

Objectives: Our goal was to develop a mechanistic mathematical model capable of predicting neutralization of multiple Aβ species in the brain, cerebrospinal fluid (CSF) and plasma during the course of Alzheimer's disease therapy with anti-Aβ monoclonal antibodies (mAbs) that possess varying PK/PD properties.

Methods: We utilized physiological and biochemical values from the literature and internal experiments and studies, including *in vitro* Crenezumab Biacore affinity data (K_d=5 nM for monomeric Aβ, 0.5 nM for oligomeric Aβ), to develop a model structure and estimate values for model parameters. Within the model structure we include mechanisms that describe mAb binding to soluble and insoluble Aβ species, efflux rates of Aβ and the mAb-Aβ complex from brain to CSF, degradation rates of Aβ and the mAb-Aβ complex within the brain and transport of Aβ across the blood brain barrier. Specifically, we consider scenarios in which the soluble Aβ pool is entirely composed of monomeric Aβ and scenarios in which the soluble Aβ pool is entirely composed of oligomeric Aβ and the impact that binding to insoluble Aβ may have on binding kinetics to each soluble species. Results generated under these scenarios are supported by further extending the model to dynamically simulate the interconversion of soluble monomeric and oligomeric Aβ species. The model is evaluated by its ability to recapitulate the observed plasma PK/PD data from Solanezumab [1] and Crenezumab [2] clinical studies.

Results: The model was able to describe the observed plasma PK/PD data following estimation of the baseline plasma Aβ, plasma Aβ clearance, PK and K_d parameters. The estimated *in vivo* mAb/Aβ binding affinity for Crenezumab is consistent with the *in vitro* K_d value (5.7 vs. 5 nM). The impact on the neutralization of soluble Aβ in brain given the affinity of the mAb to insoluble Aβ pool is also demonstrated, where, during the first ~12 months of treatment, the insoluble Aβ pool acts as a significant sink for mAb at affinities significantly greater than 5 nM.

Conclusions: Our model generated predictions that yield insight into neutralization of soluble and insoluble Aβ species in brain during anti-Aβ mAb therapy. We also developed hypotheses regarding mechanisms such as the potentially significant impact of mAb binding to insoluble Aβ pools in the brain on overall mAb/Aβ dynamics.

References:
[1] Uenaka, K. *et al.* Clin Neuropharmacology 2012.
[2] Boxer, AL. *et al.* Alzheimer's & Dementia 2010.

I-09: *Eric Fernandez* Modelling and translating head and neck radiation therapy on all three levels: in vitro, in vivo and clinical

Eric Fernandez, Frances Brightman, David Orrell and Christophe Chassagnole
Physiomics plc

Objectives: One of the most demanding tasks in pharmaceutical drug development is the capability to predict clinical outcome for a planned study based on preclinical observations. A technique such as *in silico* tumour cell population modelling can help predict the effect of anti-neoplastic agents, and therefore optimise dose and administration scheduling of these agents. Here it is our aim to demonstrate how radiation therapy mechanism of action can be translated from *in vitro* experiments to *in vivo* animal studies and then to the clinic.

Methods: Experimental radiation treatment data from in vitro [1], in vivo xenograft [2,3] and clinical efficacy studies [4] have been extracted from selected literature references. These data included FACS time series analysis of irradiated cultured cells, tumour xenograft growth rate studies and head and neck clinical tumour size from patients during the course of radiation therapy. We used these data to model irradiation mechanism of action in our VT tumour population [5] and calibrate the model for the three levels of experimental work.

Results: Using a tumour cell population model such as the VT we were able to translate the efficacy of radiation on three levels: firstly, from *in vitro* to *in vivo* and then from *in vivo* to clinical studies, without changing the underlying mechanism of action of radiation at the cellular level. The only adjustments were key parameters of the cell population structure.

Conclusions: We explored how the model could be converted to fit, using the same mechanism of action from *in vitro* to *in vivo* to clinical. We have shown that cell population structure is key to be able to describe the effect of irradiation at the three levels. This paves the way of using our VT technology to predict clinical outcomes from pre-clinical studies.

References:

[1] Warenius, H. M. *et al.* Late G1 accumulation after 2 Gy of gamma-irradiation is related to endogenous Raf-1 protein expression and intrinsic radiosensitivity in human cells. *Br. J. Cancer* **77,** 1220–1228 (1998).
[2] Matsumoto, F. *et al.* The Impact of Timing of EGFR and IGF-1R Inhibition for Sensitizing Head and Neck Cancer to Radiation. *Anticancer Res.* **32,** 3029–3035 (2012).
[3] Fatema, C. N. *et al.* Dual tracer evaluation of dynamic changes in intratumoral hypoxic and proliferative states after radiotherapy of human head and neck cancer xenografts using radiolabeled FMISO and FLT. *BMC Cancer* **14,** 692 (2014).
[4] Belli, M. L. *et al.* Characterization of volume and shape modifications of PET-positive nodes during Tomotherapy for head and neck cancer as assessed by MVCTs. *Radiother. Oncol.* **115,** 50–55 (2015).
[5] Fernandez, E. *et al.* Modeling the sequence-sensitive gemcitabine-docetaxel combination using the Virtual Tumor. in *AACR 102nd Annual Meeting, Orlando, FL* (2011). Avalilable at http://www.physiomics-plc.com/wp-content/uploads/downloads/2011/05/Poster_Oncodesign_AACR-2011_FINAL.pdf

I-10: *Natalie Filmann* Comparing the individual and the population approach in fitting heterogeneous PK/PD data of patients with chronic hepatitis B after liver transplantation

Natalie Filmann and Eva Herrmann
Goethe-University Frankfurt

Objectives. We have developed and evaluated virus kinetics models for the HBsAg-kinetics and the anti-HBs PK after liver transplantation based on existing models for chronic hepatitis B and the general Target Mediated Drug Disposition Model (TMDD-Model) [1, 2, 3, 4]. Model parameters were estimated by non-linear fitting of individual patient data. Individual fitting was used because we have focused on model building for a small, but detailed data set consisting of 18 patients who exhibit heterogeneous complex dynamics.
Aim of this study is to compare the individual and the population approach in this context.

Methods. Model parameters were estimated by non-linear fitting with MATLAB (R 2010a) using a maximum likelihood approach for individual fitting and using the population approach using nonlinear mixed-effect models in Monolix (version 4.3.3) by the SAEM algorithm, respectively.
The more detailed dataset 1 (n=18) was originally collected in the context of a prospective study [5] and was used for model building due to its richness. Datasets 2 (n=25) and 3 (n=26) were collected retrospectively and were used for model validation.

Results. The population approach leads to more stable estimates.
The individual approach allows fitting details in the observed kinetics that were exhibited by some patients and assumed to be important for model building. Fitting these details seems difficult with the population approach. A limitation of the population approach is that assumptions concerning the distributions of the residuals and random errors apply, which might be difficult to test for small datasets.

Conclusion. The individual approach seems to be more adequate for model building, whereas the population approach leads to more stable estimates and provides a valuable tool for post-hoc analyses and further validation of the model.

References:
[1] M. A. Nowak, S. Bonhoeffer, A. M. Hill, R. Boehme, H. C. Thomas and H. McDade. Viral dynamics in hepatitis B virus infection. Proceedings of the National Academy of Sciences, 93:4398–402, 1996.
[2] D. E. Mager and W. J. Jusko. General pharmacokinetic model for drugs exhibiting target mediated drug disposition. Journal of Pharmacokinetics and Pharmacodynamics, 28: 507–32, 2001.
[3] N. Filmann, J. Rosenau, M. P. Manns, H. Wedemeyer, E. Herrmann. Modeling the PK/PD of hepatitis B immunoglobulin after hepatitis B induced liver transplantation by an extended Target Mediated Drug Disposition Model. Presented at oral presentation at the 24th meeting of the Population Approach Group in Europe ; 2015 Jun 2-5; Hersonnisos, Crete, Greece. Available from www.page-meeting.org/?abstract=3454
[4] N. Filmann, J. Rosenau, M. P. Manns, H. Wedemeyer, E. Herrmann. Modeling the PK/PD of Hepatitis B immune globulin after Hepatitis B-induced liver transplantation by an extended Target Mediated Drug Disposition Model. [submitted]
[5] J. Rosenau, T. Kreutz, M. Kujawa, M. Bahr, K. Rifai, N. Hooman, A. Finger, G. Michel, B. Nashan, E. R. Kuse, J. Klempnauer, H. L. Tillmann and M. P. Manns. HBsAg level at time of liver transplantation

determines HBsAg decrease and anti-HBs increase and affects HBV DNA decrease during early immunoglobulin administration. Journal of Hepatology, 46:635–44, 2007.

I-11: *Linda Franken* Pharmacokinetics of midazolam and its metabolites in terminally ill adult patients

L.G.W. Franken, PharmD (1), A.D. Masman, MD (2,3), B.C.M de Winter, PharmD, PhD (1), B.C.P. Koch, PharmD, PhD (1), F.P.M. Baar, MD (2), D. Tibboel, MD, PhD (3,4), T. van Gelder, MD, PhD (1) and R.A.A. Mathôt, MD, PhD (5)

1 Department of Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands 2 Palliative Care Centre, Laurens Cadenza, Rotterdam, the Netherlands 3 Intensive Care, Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands 4 Pain Expertise Centre, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands 5 Hospital Pharmacy – Clinical Pharmacology, Academic Medical Centre, Amsterdam, the Netherlands

Objectives: Midazolam is a commonly used sedative drug in terminally ill adult patients and is titrated to achieve the desired level of sedation. As terminally ill patients are a very heterogeneous population with severe co-morbidity (e.g. hepatic and renal impairment) patients could potentially benefit from an individualised dose that is determined beforehand. To find clinical relevant parameters for dose individualisation we performed a pharmacokinetic study on midazolam, 1OH-midazolam (1OH-M) and 1OH-midazolam-glucuronide (1OH-MG) in adult terminally ill patients.

Methods: 192 samples from 47 patients who had received midazolam orally and subcutaneously were available. Population pharmacokinetic parameters were estimated using non-linear mixed effects modelling (NONMEM 7.2). The covariates analysed were patient characteristics, co-medication and blood chemistry levels. The predictive performance of the model was evaluated with a normalised prediction distribution errors (NPDE) analysis.

Results: The data were best described by a one-compartment model for midazolam, 1OH-M and 1OH-MG. Between-subject variability (BSV) was shown for the bioavailability of midazolam, clearance of midazolam, 1OH-M and 1OH-MG and for the volume of distribution of midazolam. The population mean estimates for midazolam, 1OH-M and 1OH-MG clearance were 9.1 L/h (BSV 46%), 48 L/h (BSV 58%) and 5.7L/h (BSV 49%) respectively. Low albumin levels corresponded with low midazolam clearance and explained 19 % of the BSV in midazolam clearance. 1OH-MG clearance was correlated with the estimated glomular filtration rate (eGFR) explaining 40% of the BSV in 1OH-MG clearance. The NPDE analysis showed good model predictability with the distribution of the NPDEs not significantly deviating from a normal distribution (P-value 0.789).

Conclusions: The population pharmacokinetics of midazolam and its two major metabolites were accurately quantified. A decreased eGFR resulted in lower clearance of 1OH-MG and could therefore result in increased sedation. Low albumin levels were associated with decreased midazolam clearance, probably as a result of inflammatory response. CRP as a covariate had a similar effect as albumin yet less significant. eGFR and albumin might be useful clinical parameters to develop an individualized dosing regimen. Additional studies on the pharmacodynamic effects of midazolam in this population are recommended.

I-12: *Jonathan French* A case study in comparing cognitive development across populations

Jonathan L. French (1), Amy Racine (2), Stef van Buuren (3), Jonas Haggstrom (4), and the Lifecycle, Auxology and Neurocognitive Development Surge Team (5) – representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community
(1) Metrum Research Group, Tariffville, CT, USA. (2) Novartis, Inc., Basel., Switzerland, (3) TNO, Utrecht, Netherlands, (4) Holy Diver Consulting, Stockholm, Sweden, (5) Sponsored by the Bill & Melinda Gates Foundation, Healthy Birth, Growth and Development Initiative.

Objectives: Assessment of neurocognitive development during the first 1000 days of life is important, particularly in children in low- and middle-income countries (LMIC). There are a variety of instruments used for these assessments, most of which are based on a defined set of tasks for the child to perform. Tasks are typically scored as a set of ordered categories. It has been proposed that the development score (D-score) is one way to integrate data collected using different scales and across different populations [1,2]. The objectives of this work were to evaluate the assumptions underlying the D-score using data from an LMIC population and to assess if the D-score can be used for between-population comparisons.

Methods: We connect a child's D-score to the observed longitudinal outcomes through a Rasch model [1], a type of item-response theory model. Key assumptions of the Rasch model include invariance to the set of items used and common item-level difficulty across populations. Using data from a high income country (HIC) longitudinal study, the item-level difficulty values were previously estimated [1,2]. We evaluate the assumption of parameter invariance by comparing the estimated D-score based on the full set of items and matching items in the LMIC study instrument. We use discrimination plots to compare item difficulty and item discrimination across studies. Finally, we compare the longitudinal D-scores between the HIC and LMIC study populations.

Results: Comparison of the D-score based on the full-set and matched-set of items in the HIC study shows high correlations both overall and by age. Discrimination plots reveal that while many of the assumptions of the Rasch model hold, some difficulty parameters may differ across HIC and LMIC populations. These differences appear to be driven by items relating to language and motor skills. Compared to the HIC study, the D-scores in the LMIC study show average development at 6 months, higher than average scores at 15 months, and lower than average scores at 24 months.

Conclusions: The D-score shows promise for facilitating comparisons across populations. However, it has not been clearly validated for this purpose. While the D-score appears to be invariant to the choice of items, the item-level difficulties may depend on the population and/or instrument used to collect them. Additional work is needed to more fully evaluate the D-score, including comparisons using additional populations and neurocognitive development instruments.

References:

[1] Jacobusse G, Van Buuren S, and Verkerk PH. An interval scale for development of children aged 0-2 years. *Stat Med* 2006; 35(13): 2272-2283
[2] Van Buuren, S. Growth charts of human development. *Stat Methods Med Res* 2014; 23(4): 346-368

I-13: *Nicolas Frey* Model-based meta-analysis of amyloid plaque reduction in Alzheimer's disease patients to identify new Phase 3 doses and dosing regimens for Gantenerumab

Nicolas Frey, Ronald Gieschke, Cornelia Weber, Johann Laurent, Carsten Hofmann, Sylvie Retout
Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: A pre-specified futility analysis of SCarlet RoAD (SR), a Phase 3 of the anti-Aβ antibody gantenerumab (GAN) in prodromal Alzheimer's disease (AD), estimated a low probability for trial success due to a lack of significant drug effect and dosing was discontinued. Further investigations highlighted an exposure-AD clinical scales relationship in a sub-group of fast progressor patients [1] and a signal of brain amyloid plaque removal activity in a PET sub-study (N=114, 14% of the SR patients). This signal was rather small (-10% PET decrease at 2 years (y) in the highest exposure group), suggesting an under-dosing. At the same time, aducanumab (ADU), a very similar drug investigating higher doses, reported up to -20% PET decrease at 1 y in the highest dose group (N=123), significantly associated with a slowing decline on AD scales [2]. Based on both SR data and ADU PET data, we proposed to build an exposure – PET model to identify new doses / dosing regimens for the GAN program.

Methods: Population pharmacokinetic/pharmacodynamic (PK/PD) analyses were performed on combined GAN and ADU data. The final PKPD dataset included 237 patients and 693 PET observations, collected at baseline, weeks 20, 60 and 100 for GAN and at baseline, weeks 26 and 54 for ADU. Direct and indirect responses were investigated, as well as different PKPD relationships from linear to sigmoid. In addition to goodness of fit tests, visual predictive checks (VPC) of the selected model were performed, per dose and per exposure groups, to test its appropriateness when predicting the GAN and ADU dataset, either pooled or separately. Last, combined with a safety model [3], simulations were conducted to investigate up-titration dosing regimens balancing both PET response (-20% at 2y) and safety criteria.

Results: The exposure-PET relationship was best described by a power model combined with an effect compartment. No bias in the predicted PET values was observed. The model captures both the central tendency and the between subject variability of both GAN and ADU PD in the target AD patients. Using simulations, up-titration dosing regimens balancing plaque removal and safety events were identified.

Conclusions: A robust model of exposure - amyloid brain plaque removal relationship was built using a meta-analysis of both internal and external data. It informed up-titration dosing regimens for higher Phase 3 success likelihood; they are currently investigated in GAN ongoing studies.

References:

[1] Retout, S et al. Abstr PAGE 25, Lisbon, Portugal (2016)
[2] Sevigny, J et al, 67th Annual Meeting of the American Academy of Neurology, Washington DC, US (2015)
[3] Gieschke, R et al. Abstr PAGE 25, Lisbon, Portugal (2016)

I-14: *Aline Fuchs* Simulations to simplify gentamicin dosing regimens for neonates and young infants when referral is not possible in developing countries

Fuchs Aline (1), Gotta Verena (1), Johannes Van Den Anker (1,2,3), Marc Pfister (1)
(1) Division of Paediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel, Switzerland, (2) Intensive Care and Department of Surgery, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands, (3) Division of Clinical Pharmacology, Children's National Health System, Washington, DC, USA

Objective: To provide a simple gentamicin dosing regimen recommendation for outpatient treatment of neonates and young infants (0 – 59 days old) with possible serious bacterial infection when referral is not an option. The simple dosing regimen should be based on three body weight bands allowing effective and safe exposure in a majority of these infants.

Methods: Target peak concentrations of gentamicin relative to the minimum inhibitory concentration (MIC) was set to > 5 assuming a MIC value of 0.5 mg/L, whereas target trough concentrations was set to < 2 mg/L to maximize efficacy while mitigating the risk of drug related nephro- and oto-toxicity. The following dosing scenarios were evaluated: doses ranging from 8 to 14 mg, 14 to 20 mg and 20 to 26 mg based on three weight groups ([1.5 – 2.4], [2.5 – 3.9], [4 – 6] kg) respectively, administered every 24, 36, and 48 hours. Gentamicin exposure was evaluated by simulation after the first intramuscular (IM) dose and after seven consecutive IM doses utilizing a published pharmacokinetic model[1]. The simulated population of neonates and infants comprised 450 virtual neonates with realistic combinations of weight (1.5 kg to 6.0 kg) and postnatal age (0 to 59 days) based on WHO growth charts. Each of these 450 patients was simulated 100 times to account for both inter- and intra-individual variability.

Results: Given predefined target peak and trough concentrations, simulations indicated that doses of 8, 16 and 24 mg every 24 hours bring > 80% of patients in the desired target ranges for 1.5 – 2.4 kg, 2.5 – 3.9 kg and 4.0 – 6.0 kg weight bands, respectively. After seven doses administered every 24 hours, no obvious accumulation of gentamicin was found, likely due to post-natal, time dependent maturation resulting in an increase in drug clearance. If a peak concentration of 8 mg/L is considered, the 1.5 – 2.4 kg would require doses of 10 mg to reach an appropriate peak concentration in 80% of patients. It would result in 17% of infants with a trough concentration > 2mg/L over a 24h dosing interval.

Conclusion: Based on pharmacokinetic simulations, doses of 8, 16 and 24 mg every 24 hours for the 1.5 – 2.4 kg, 2.5 – 3.9 kg and 4 – 6 kg weight bands respectively, are expected to be appropriate for most patients in this context. This simplified scheme of administration assumes that a peak concentration of 5 mg/L and a trough concentration < 2 mg/L are effective and safe respectively.

Reference:
[1] Thomson AH, Kokwaro GA, Muchohi SN et al. Population pharmacokinetics of intramuscular gentamicin administered to young infants with suspected severe sepsis in Kenya. Br J Clin Pharmacol. 2003 Jul;56(1):25-31.

I-15: *Saskia Fuhrmann* Generic PBPK model to predict preclinical and clinical PK of antibodies

Saskia Fuhrmann (1,4), Charlotte Kloft (3) and Wilhelm Huisinga (2)
(1) Institute of Biochemistry, Universitaet Potsdam, Germany; (2) Institute of Mathematics, Universitaet Potsdam, Germany; (3) Institute of Pharmacy, Dept. Clinical Pharmacy & Biochemistry, Freie Universitaet Berlin; (4) Graduate Research Training Program PharMetrX: Pharmacometrics & Computational Disease Modelling, Freie Universitaet Berlin and Universitaet Potsdam, Germany

Objectives: One of the primary applications of PBPK modeling is to predict efficacious and non-toxic clinical dose and human PK for new chemical and biological entities (NCEs, NBEs). *In silico* methods to predict tissue-to-plasma partition coefficients have significantly advanced the use of PBPK models for NCEs. The routine application of PBPK models to predict PK of NBEs, in particular monoclonal antibodies (mAbs), however is still challenging [1]. Antibody biodistribution coefficients (ABCs)[2] strongly support extrapolation of mAb PK between species. The objective of our study was to evaluate the feasibility of a generic PBPK modeling approach incorporating ABCs as a general approach to study mAb PK in different preclinical species and humans. The focus was on mAbs binding to soluble targets.

Methods: PK data of 22 mAbs of IgG isotype from mice, rat and humans were obtained from literature and analyzed with the generic PBPK model parameterized by ABC values [3]. The only unknown parameter(s) relate to species-dependent clearance processes. In most cases, also in the presence of target, linear PK for mAbs was observed - depending on dose range and target concentrations. In the dose-linear range, only linear total clearance was estimated. For mAb PK data resulting from a large dose range, we estimated both, linear and nonlinear clearance, with the generic PBPK approach extended by a Michaelis-Menten TMDD model.

Results: Estimates of the total linear mAb clearance in humans were similar for different mAbs and ranged from 0.1 to 0.5 l/day, which is comparable to the clearance of endogenous IgG and within the reported range for mAbs [4]. The median clearance 0.223 l/day can serve as a default value for linear total clearance to obtain good predictions for PK of mAbs binding to soluble targets in humans. Often, also in the presence of a target, the unspecific clearance is the dominating clearance process; and only for lower concentrations, nonlinear PK was observed with target-mediated clearance dominating over the unspecific clearance.

Conclusions: We showed that a generic PBPK approach parameterized by ABC values allows to study mAb PK across species with only clearance as unknown parameter. For a given mAb the generic PBPK model with median linear plasma clearance can provide reference prediction, e.g. to study the extent of target-mediated elimination.

References:

[1] H. M Jones et al. The AAPS Journal, 15: 377-387, 2012.
[2] Shah et al. mAbs, Vol.5: 297-305, 2013.
[3] W.Huisinga, S.Fuhrmann, L.Fronton, B.F.Krippendorff Target-Driven Pharmacokinetics of Biotherapeutics in *Application of ADME and Translational PK/PD in the development of therapeutic biologics* (Eds. H. Zhou and F.-P. Theil) Wiley, 2015.
[4] N. Dirks et al. Clinical pharmacokinetics, 49: 633-659, 2010.
[5] L. Fronton et al. J Pharmacokinet Pharmacodyn, 41: 87-107, 2014.
[6] B. Kuang et al. Bioanalysis, 2: 1125-1140, 2010.

I-16: *María García-Cremades* A comparison of different model-based approaches to scale preclinical to clinical tumour growth inhibition in gemcitabine-treated pancreatic cancer

Maria Garcia-Cremades (1), Celine Pitou (2), Philip W Iversen (3), Iñaki F Troconiz (1)
(1)Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona, Spain, (2) Global PK/PD & Pharmacometrics, Eli Lilly and Company, Windlesham, Surrey, UK, (3) Lilly Research laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA.

Objectives: To compare four translational scaling approaches to predict clinical response to gemcitabine treatment in pancreatic cancer patients using preclinical data obtained in xenograft tumour-bearing mice. This work formed part of pillar 3 in working package I (models in oncology) within the IMI7 founded project Drug Disease Models Resource (DDMoRe).

Methods: Pharmacokinetic/Pharmacodynamic models for Gemcitabine describing longitudinal tumour size data have been developed in xenograft mice, for different pancreatic cell lines, and in patients with pancreas cancer (1, 2). The information used to develop the translational simulation exercise comprises for both mice and human: Treatment (dose, dosing schedule), Pharmacokinetics (clearance, volume of distribution, drug exposure), Tumour dynamics (tumour proliferation rate) and Pharmacodynamics (drug-effects & resistance). Based on the above information, the following approaches were evaluated for predictive translational performance:

1. Direct comparison between preclinical and clinical model parameters.
2. Direct comparison between preclinical and clinical maximal tumour growth inhibition (TGI) and tumour growth delay (TGD).
3. Allometric scaling of the pharmacokinetic and pharmacodyamics parameters.
4. Simulations of tumour growth inhibition in patients using Treatment and Pharmacokinetics, from human and Tumour dynamics and Pharmacodynamics from mice. (3).

Results: Preliminary results show that direct comparison between preclinical and clinical parameters and descriptors is not possible due to the disparity of doses, schedules and structural models used for the trials. Meanwhile descriptors simulated with the combined preclinical-clinical model (such as TGI or TGD), appeared to provide better link; in fact the predicted percentage of TGI coupling patient dosing and PK with mice derived drug effect parameters resulted close with TGI predictions found with the human PKPD model (> 100 % TGI according to (3) in both cases). The results were more promising in the case of the panc1 xenografts than the rest of tumour cells lines implanted in mice.

Conclusions: Currently the preclinical tumor growth inhibition modelling work is often used more qualitatively then quantitatively to predict the clinical results. In this work, we compare different translational approaches which could lead to more quantitative alternatives. The same exercise will also be performed with the gemcitabine-treated ovarian cancer.

References:
[1] PAGE 23 (2014) Abstr 3163 [www.page-meeting.org/?abstract=3163]
[2] PAGE 24 (2015) Abstr 3343 [www.page-meeting.org/?abstract=3343]
[3] Wong H.et al. Clin Cancer Res 2012; 18:3849-3855

I-17: *Peter Gennemark* Unravelling the pharmacokinetic interaction of ticagrelor and MEDI2452 (ticagrelor-antidote) using mouse data

Peter Gennemark (1), Mark Penney (2), Susanne Pehrsson (1), Ann-Sofie Sandinge (1), Annika Janefeldt (1), Sufyan Maqbool (2), Shimona Madalli (3), Joanne Goodman (2), Sven Nylander (1), Joachim Almquist (4, 5)
(1) Cardiovascular and Metabolic Diseases, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Mölndal, Sweden; (2) Clinical Pharmacology and DMPK, MedImmune, Cambridge, UK; (3) Cardiovascular and Metabolic Diseases Research, MedImmune, Cambridge, UK; (4) Fraunhofer-Chalmers Centre, Chalmers Science Park, Gothenburg, Sweden; (5) Systems and Synthetic Biology, Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden.

Objectives: The investigational ticagrelor-neutralizing antibody fragment MEDI2452 has been developed to rapidly and specifically reverse the antiplatelet effects of ticagrelor [1]. Due to the dynamic interaction of ticagrelor, the ticagrelor active metabolite (TAM), and MEDI2452, analysis of pharmacokinetic (PK) data becomes non-trivial. The main objective of the present work is to better understand the PK of ticagrelor, TAM, and MEDI2452, and in particular to be able to predict free plasma concentrations that can bind to and inhibit platelet P2Y12 of ticagrelor and TAM.

Methods: The modelling process consists of three main steps: i) set-up a mathematical model of the combined ticagrelor-MEDI2452 PK in the mouse based on data of separately administered ticagrelor and MEDI2452, and on assumptions supported by literature; ii) validate and refine the model on several different combined ticagrelor-MEDI2452 PK data sets not used for setting up the model; and iii) use the model to understand the complex PK resulting from the ticagrelor-MEDI2452 interaction, and to predict free levels of ticagrelor and TAM and let these predictions drive a pharmacodynamic (PD) turn-over model under different experimental designs.

Results: We propose a mechanistic PK model, including a special observation model for post-sampling equilibration, which is validated and refined using four different combined ticagrelor-MEDI2452 mouse in vivo treatment data sets. A comparison against alternative models strengthen our a priori belief that MEDI2452-bound ticagrelor is primarily eliminated together with MEDI2452 in the kidney, and not recycled to the plasma, thereby providing a key assumption for the extrapolation to humans. The model predicts free ticagrelor and TAM plasma concentrations, which, in turn, drive a PD model that successfully predicts platelet inhibition level.

Conclusion: The proposed PK model of ticagrelor, TAM, and MEDI2452 has been validated on several mouse data sets and is useful for predicting free plasma concentrations of ticagrelor and TAM. The model significantly improves PK and PD understanding, experimental design, and translational confidence.

References:
[1] Buchanan, A. et al. Structural and functional characterization of a specific antidote for ticagrelor. Blood 125, 3484-90 (2015).

I-18: *Eva Germovsek* Pharmacokinetic-pharmacodynamic (PKPD) modelling of meropenem in plasma and cerebrospinal fluid (CSF) in infants with late-onset sepsis and/or bacterial meningitis

Eva Germovsek (1, 2), Irja Lutsar (3), Karin Kipper (3), Mats O Karlsson (2), Joseph F Standing (1) on behalf of the NeoMero consortium

(1) Department of Infection, Inflammation and Rheumatology, Institute of Child Health, University College London, UK; (2) Department of Pharmaceutical Biosciences, Uppsala University, Sweden; (3) Department of Microbiology, University of Tartu, Estonia

Objectives: Meropenem is used off-label in the treatment of late-onset sepsis (LOS) and meningitis in infants. We aimed to develop a population pharmacokinetic (PK) model for meropenem plasma and CSF concentrations, and use it for dosing recommendations in infants <3 months. We also aimed to investigate if the PKPD target of 40% of time above the minimal inhibitory concentration (MIC) (t>MIC) [1] is sufficient for infants.

Methods: Meropenem was given at 20 mg/kg (LOS) or 40 mg/kg (meningitis) as a 30-min infusion every 8, or every 12h in infants <32 weeks gestational age (GA) and <2 weeks postnatal age (PNA). NONMEM 7.3 was used. Firstly, different structural and residual error models were fitted to the plasma data. Allometric weight scaling and a function describing renal function maturation [2] were used *a priori*, and serum creatinine (SCr) and PNA were tested on clearance (CL). Then, a CSF compartment was added, and plasma-CSF clearance (Q_CSF) and fraction of meropenem penetration from plasma to CSF (f_CSF) were estimated. The effect of markers of central nervous system inflammation on f_CSF was investigated. Monte-Carlo simulations (n=1000) were used to generate the probability-of-target-attainment (PTA) curves. Finally, the PK model was combined with an *in vitro* PKPD model [3], describing the effects of meropenem on *Pseudomonas aeruginosa*.

Results: 167 infants with median (range) GA 33.3 (22.6-41.9) weeks, and PNA 13 (1-90) days at enrolment provided 401 plasma and 78 CSF samples. The final PK model for plasma was a 1-compartment model, SCr proved significant on CL, and CSF protein concentration on f_CSF. A Box-Cox power transformation [4] was used to address the non-normally distributed residuals. The parameter values (mean (%SE)) for a typical infant (weight=2.12 kg, postmenstrual age=37.4 weeks, SCr=32 µmol/L) were: CL=0.48 (5.2%) L/h, volume of distribution 1.18 (5.6%) L, Q_CSF=0.0012 (24.3%) L/h, f_CSF=0.085 (18.8%). Diagnostic plots showed adequate descriptive and simulation properties of the model. Dosing regimens used in the study were appropriate if MIC <4mg/L (LOS) or <1mg/L (meningitis) for a target of 40% t>MIC; however, this target overpredicted meropenem effect, when compared to the *in vitro* target of 2log kill at 24h.

Conclusion: A PK model for plasma and CSF meropenem data in young infants with LOS and/or meningitis was developed. The dosing regimen used in the study was shown appropriate for susceptible pathogens, but 40% t>MIC appeared insufficient for severely immunocompromised infants.

Acknowledgements: The NeoMero study was funded as a part of the European FP7 Programme.

References:

[1] Drusano, Nat Rev Microbiol. 2004; 2(4):289-300.
[2] Rhodin *et al*., Pediatr Nephrol, 2009. 24(1):67-76.

[3] Mohamed *et al*., J Antimicrob Chemother. 2016; 1-12.
[4] Dosne *et al*., J Pharmacokinet Pharmacodyn. 2015; 1-15.

I-19: *Andy Gewitz* PK/PD Modeling of Tuberculosis for Identification of Biomarkers Associated with Treatment Duration

Andrew Gewitz (1), Marc Weiner (2), Ron Keizer (3), William MacKenzie (4), Melissa Engle (2), William Whitworth (4), John Johnson (5), Pheona Nsubuga (6), Payam Nahid (1), Nhung Viet Nguyen (7), Charles Peloquin (8), Kelly Dooley (9), Susan Dorman (9), an
(1) University of California, San Francisco, CA (2) UTHSC, San Antonio, TX (3) InsightRX, San Francisco, CA (4) Center for Disease Control, Atlanta, GA (5) Case Western Reserve University, Cleveland, OH (6) Uganda-Case Western Reserve University Research Collaboration, Kampala, Uganda (7) National Tuberculosis Program, Hanoi, Vietnam (8) University of Florida, Gainesville, FL (9) Johns Hopkins University, Baltimore, MD

Objectives: Treatment duration shortening is a major priority for current Tuberculosis (TB) drug development, yet recent clinical trials have failed to achieve this goal when testing shorter regimens in drug-sensitive TB patient populations. To identify putative sets of biomarkers that might facilitate stratification of patients by treatment duration, we developed integrated pharmacokinetic-pharmacodynamic (PK/PD) models of the outcome time-to-stable culture conversion as measured by Mycobacterial Growth Inhibitor Tube (MGIT) assay. Specifically, we wished to (i) characterize the relationship between MGIT assay dynamics and the above outcome in participants enrolled in either of two Phase 2 studies [1-2], and (ii) examine the effects of PK and clinical biomarkers on model parameters suggestive of possible shortening of treatment duration.

Methods: We developed longitudinal nonlinear mixed-effects PK/PD models using data from two randomized trials, the first a two-arm study comparing RFP and standard of-care (rifampin, RIF), and the second involving dose-ranging of RFP vs. RIF (n_{RIF} =320, n_{RPT} = 516, combined). Time-shifted logistic models were best described the dynamics of MGIT assay time-to-stabe conversion in both settings. Time-to-stable conversion was approximated using our model, and the effects of baseline biomarkers were assessed.

Results: Baseline smear grade and productive cough at entry were independently associated with time-to-stable conversion as derived from our model for RIF. For the model for RPT, baseline smear grade, cough grade at study entry, chest x-ray extent, and derived drug exposure (AUC) were independently associated with time-to-stable conversion, whereas dosage effects (both fixed and weight-based) were negligible. Further model simulations suggest, e.g., that for RIF, 95% of patients with high baseline smear grade and productive cough stably converge within 13 weeks versus within 9 weeks for 95% of patients with low smear grade and no cough at study entry.

Conclusions: Our results suggest that various baseline patient characteristics can be used to prospectively stratify patients by treatment duration in clinical TB studies, and highlight the general utility of PK/PD modeling to assess exposure-response relations and guide design of future clinical trials by identifying factors that may aid in predicting therapeutic response at earlier time points.

References:

[1] Dorman SE, Goldberg S, Stout JE, et al. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the tuberculosis trials consortium. *J Infect Dis* 2012; **206:** 1030–40.
[2] Dorman SE, Savic RM, Goldberg S, et al. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial. *Am J Respir Crit Care Med* 2015; **191**: 333–43.

I-20: *Ekaterina Gibiansky* Population Pharmacokinetic of Obinutuzumab (GA101) in Patients with Chronic Lymphocytic Leukemia (CLL), Follicular Lymphoma (FL), Other Indolent Non-Hodgkin's Lymphoma (iNHL) Subtypes, Diffuse Large B-cell Lymphoma (DLBCL), and Mantle Cell Lymphoma (MCL)

Ekaterina Gibiansky (1), Leonid Gibiansky (1), Michael Brewster (2), Candice Jamois (3), Vincent Buchheit (3), Nicolas Frey(3)
(1) QuantPharm LLC, North Potomac, MD, USA; (2) Roche Products Ltd, Welwyn, UK; (3) F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: Obinutuzumab (Gazyva, G), approved for treatment of CLL and FL [1], is a humanized type II anti-CD20 monoclonal antibody with a glycoengineered Fc region. G population PK model for patients with CLL and NHL was established earlier [2]. The aim of the analysis was to update the model with new data of patients with DLBCL and MCL and to identify covariates of G exposure.

Methods: Serum concentrations (16,301) of 961 patients (6 Phase I-III trials) were analyzed. A 2-compartment population PK model with time-dependent clearance [$CL=CL_{inf}+CL_{T}\cdot\exp(-k_{des}t)$] described G PK. The full model approach was used for covariate model development. Diagnostics plots and various predictive check procedures were used for model evaluation.

Results: Typical G CL_{inf}, CL_T, central and peripheral volumes, and inter-compartment clearance were CL_{inf} =0.074 L/day, CL_T=0.154 L/day, V_C=2.72 L, V_P=1.23 L, and Q=1.32 L/day. CL_{inf}, V_C, and V_P increased with body weight. CL_{inf}, V_C, and CL_T were 18%, 19%, and 45% higher in males. CL_{inf} decreased with age and serum albumin, and increased with baseline tumor size (TS). CL_T also increased with TS, leading to initially lower exposure in patients with high TS. For patients with iNHL and DLBCL, differences in steady-state exposure due to demographics and TS were within 35% for respective dosing regimens.

Typical CL_T declined with half-life $t_{1/2}$=6.3 days; thus, CL declined to CL_{inf} after a month of dosing. Simulations showed that for the proposed dosing regimens (1000 mg IV Q3W or Q4W with additional doses on Days 8 and 15 of cycle 1), G concentrations reach steady-state levels after cycle 1.

CL_{inf} was 47%, 107%, and 38% higher for CLL, MCL, and SLL, compared to iNHL or DLBCL. CL_T was 125% and 180% higher for CLL and MCL compared to other tumor types. CL_T declined slower ($t_{1/2}$=21 day) in MZL. Simulations of iNHL dosing regimen indicated that at the end of the Induction period (cycle 6), AUC_τ and C_{trough} were 15-18% higher in patients with MZL and 27-36% lower in patients with SLL, compared to FL. Steady-state exposure during Maintenance was nearly identical for MZL and FL, but was 33-50% lower for SLL.

k_{des} was higher with concomitant fludarabine/cyclophosphamide ($t_{1/2}$=2.4 days), and lower with bendamustine (10.7 days) or CHOP (20.4 days). However, more frequent dosing of G when administered with CHOP (Q3W) prevented lower G exposures.

Conclusions: The updated model described G PK for different tumor types and concomitant chemotherapies.

References:

[1] GAZYVA prescribing information. http://www.gene.com/download/pdf/gazyva_prescribing.pdf.
[2] E. Gibiansky, L. Gibiansky, D. Carlile, C. Jamois, V. Buchheit, N. Frey, Population Pharmacokinetics of Obinutuzumab (GA101) in Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma and Exposure-Responses in CLL, CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e144; doi:10.1038/psp.2014.42.

I-21: *Leonid Gibiansky* vc-MMAE antibody-drug conjugates: a unified model describes pharmacokinetics of eight different compounds

Leonid Gibiansky (2), Matts Kågedal (1), Jian Xu (1), Nina Wang (1), Charles Chen (1), Sandhya Girish (1), Jin Jin (1), Chunze Li (1)
(1) Genentech, Inc., South San Francisco, CA; (2) QuantPharm LLC, North Potomac, MD

Objectives: ADCs developed using Vc-MMAE platform share the same antibody technology, linker, and toxin (MMAE). The similarity of ADC structures resulted in similar PK properties. The goal of the analysis was to develop a mega model that simultaneously described antibody-conjugated MMAE (acMMAE) data from multiple ADCs, and assess differences and similarities of model parameters and predictions among different compounds.

Methods: Clinical data of 8 ADCs were obtained from 8 studies with ADC doses ranging from 0.1 to 3.2 mg/kg every 3 weeks (Q3W). Initially, data were treated as coming from the same ADC. Models with time-dependent clearance (CL) and parallel linear and Michaelis-Menten (MM) elimination were explored. Effects of weight, sex, and dose were evaluated by inclusion in the model. After the unified covariate model was developed, differences in model parameters between ADCs were investigated. A series of mega-models, from the model with all common parameters to the model with all compound-specific parameters were developed. Alternatively, the inter-compound variability was described explicitly using the third random effect level implemented using LEVEL option of Nonmem 7.3. Visual predictive checks (VPC) were used to assess ability of the models to predict PK for each compound.

Results: A two-compartment model with time dependent CL; CL and central volume (VC) increasing with weight; VC higher for males; and CL mildly decreasing with the dose described acMMAE PK of 8 ADCs. MM elimination had only minor effect on PK and was not included in the model. Time-dependence of CL had no effect beyond the first dosing cycle. The model with all parameters shared by all compounds provided reasonable acMMAE predictions and VPC plots for all compounds. For the model with all compound-specific parameters, CL and VC were similar among ADCs, with the inter-compound variability of 17% and 7%. Similar results (15% and 5%) were obtained when the inter-compound variability was described using LEVEL option. Differences among ADCs were minor relative to the inter-subject variability.

Conclusions: The population mega-model successfully described acMMAE PK of 8 ADCs. PK of acMMAE are largely comparable across different vc-MMAE ADCs. The model can be applied to predict properties of ADCs under development, estimate individual exposure for the subsequent PK-PD analysis, and propose optimal dosing regimens. PK of acMMAE is similar among ADCs of the same platform.

I-22: *Anais Glatard* Influence of UGT2B7 polymorphism on varenicline clearance in a cohort of smokers from the general population

Anaïs Glatard (1,2), Monia Guidi (2,3), Maria Dobrinas (1), Jacques Cornuz (4), Chantal Csajka (2,3)* and Chin B. Eap (1,3)*

*(1) Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Hospital of Cery, Prilly, Switzerland (2) Division of Clinical Pharmacology, Service of Biomedicine, Department of Laboratory, Lausanne University Hospital, Lausanne, Switzerland (3) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland (4) Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland *joint corresponding authors*

Objectives: Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor, and is widely used for smoking cessation. 90% of the dose administered is eliminated unchanged in urine, notably via OCT2 and the most abundant metabolite is obtained by glucuronidation via UGT2B7[1]. Varenicline has been proven to be generally effective at 1 mg twice daily[1,2], however inter-individual variability in the quitting rate is observed[3,4], that might be linked to the high reported variability in blood concentrations. The aim of this work was to assess whether genetics factors can explain a part of the variability in varenicline blood levels and therefore its effectiveness.

Methods: Varenicline blood levels were collected in 82 patients during a smoking cessation program with information on abstinence and scores of cigarette withdrawal symptoms. Nineteen single nucleotide polymorphisms of the OCT2, UGT2B7 and nuclear receptors that regulate OCT transporters were selected for analysis and genotyped using the Cardio-MetaboChip (Illumina). The structural PK model development and the covariate analysis were performed by non-linear mixed effect modelling using NONMEM®. Associations between varenicline exposure, defined by the model-based cumulated area under the concentration–time curve (AUCcum), and abstinence as well as withdrawal scores were evaluated in R.

Results: A one-compartment model with first order absorption and elimination appropriately described the 121 varenicline concentrations. Varenicline systemic clearance (CL) was 8.51 L/h (CV 25.7%), the volume of distribution was 228 L and the absorption rate was fixed to 0.98 h^{-1}. An allometric power function with the allometric exponent fixed to 0.75 described adequately the relationship between CL and body weight (BW), leading to a 68% increase in CL upon BW doubling. *UGT2B7* rs7439366 C/C carriers were found to have 21% higher CL than T/T and C/T carriers. BW and the *UGT2B7* rs7439366 explained 14% and 9% of the inter-individual variability on CL, respectively. AUCcum had a significant positive effect on abstinence rate (OR=12.7; 95%CI=4.3-47.0). No association was found between withdrawal scores and AUCcum.

Conclusions: BW and a genetic polymorphism of *UGT2B7* significantly contribute to varenicline plasma concentrations variability. Our results indicate that cumulative exposure to varenicline is associated with abstinence and that dosage titration based on response might increase treatment sucess.

References:

[1] Faessel HM, Obach RS, Rollema H, et al. A Review of the Clinical Pharmacokinetics and pharmacodynamics of Varenicline for Smoking Cessation. Clin Pharmacokinet 2010 ; 49(12) :799-816
[2] Reus VI, Obach RS, Coe JW, et al. Varenicline: new treatment with efficacy in smoking cessation. Drugs Today (Barc). 2007;43(2):65-75.
[3] Cahill K, Stead LF, Lancaster T, et al. Nicotine receptor partial agonists for smoking cessation. Cochrane

Database Syst Rev. 2012;4:CD006103
[4] Fiore MC, Baker TB. Treating Smokers in the Health Care Setting. N Engl J Med. 2011;29;365(13):1222-31

I-23: *Britta Goebel* Modeling & Simulation of Long-Term Body Weight Loss during Obesity Pharmacotherapy

Britta Göbel (1), Stefanie Keil (1), Thomas Klabunde (1), Arjun Sanghvi (2), Joachim Tillner (1), Kevin D Hall (2)

(1) Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany; (2) National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

Objectives: Obesity pharmacotherapy can lead to clinically meaningful long-term body weight loss [1]. In early Proof-of-Concept studies, drug effects on body weight are often measured for a period of few weeks only. However, the question arises how body weight changes develop over a long period of treatment, i.e., several years. This knowledge is crucial to decide early in the clinical program, if the targeted weight loss after long-term treatment can be reached. In humans, most obesity drugs work by decreasing metabolizable energy intake. However, quantification of energy intake changes during long-term obesity pharmacotherapy has been prevented by the limitations of self-report methods of measuring energy intake or extrapolation from short-term meal tests [2].

Methods: A validated mathematical model of human metabolism was used to provide the first quantification of metabolizable energy intake changes during long-term obesity pharmacotherapy using body weight data from randomized, placebo-controlled trials that evaluated 14 different drugs or drug combinations [3,4,5,6]. For novel weight reducing drug candidates with a body weight time profile only covering the first weeks of treatment, the long-term body weight loss was estimated applying a quantitative systems pharmacology model.

Results: Changes in metabolizable energy intake during obesity pharmacotherapy were reasonably well described by an exponential pattern, with early large changes in metabolizable energy intake followed by a slow transition to a smaller persistent drug effect. The high correlation between early and late drug effects on energy intake suggests that short-term data can be used to estimate long-term weight outcomes.

Conclusions: Repeated body weight measurements along with a mathematical model of human metabolism can be used to quantify changes in metabolizable energy intake during obesity pharmacotherapy. The calculated metabolizable energy intake changes followed a universal exponential pattern, and hence different drugs can be evaluated and compared using a common mathematical framework. Moreover, the described approach allows translating short-term drug effects into long-term estimations of body weight loss by means of a systems pharmacology approach.

References:

[1] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA 2014;311:74-86.
[2] Schoeller DA, Thomas D, Archer E, et al. Self-report-based estimates of energy intake offer an inadequate basis for scientific conclusions. Am J Clin Nutr 2013;97:1413-1415.
[3] Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. Lancet 2011;378:826-837.
[4] Hall KD, Chow CC. Estimating changes in free-living energy intake and its confidence interval. Am J Clin Nutr 2011;94:66-74.
[5] Sanghvi A, Redman LM, Martin CK, Ravussin E, Hall KD. Validation of an inexpensive and accurate mathematical method to measure long-term changes in free-living energy intake. Am J Clin Nutr.

2015;102(2):353-358.
[6] Goebel B, Sanghvi A, Hall KD. Quantifying Energy Intake Changes During Obesity Pharmacotherapy. Obesity 2014;22(10):2105-2108.

I-24: *Bojana Golubovic* Population modelling of sirolimus data available from routine therapeutic drug monitoring

Golubovic B (1), Vucicevic K (1), Jovanovic M (1), Radivojevic D (2) , Kovacevic Vezmar S (1), Prostran M (3), Miljkovic B (1)

(1) Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia (2) Nephrology Clinic, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia (3) Department of Pharmacology, Clinical Pharmacology and Toxicology, University of Belgrade - School of Medicine, Belgrade, Serbia

Objectives: The purpose of this study was to develop and validate a population pharmacokinetic model using routine therapeutic drug monitoring (TDM) data.

Methods: The data obtained by routine TDM of sirolimus in 25 patients over a period of one year from sirolimus treatment initiation, were collected retrospectively from patient records. Population analysis was performed using a nonlinear mixed effects modeling software NONMEM® (ver. 7.3). A one-compartment pharmacokinetic model with first-order absorption and elimination (1-COMP) with fixed volume of distribution (Vd/F) and absorption rate constant (k_a) on literature values, a 1-COMP with use of priors for Vd/F and k_a and their variability and two-compartment model with first-order absorption and elimination with use of priors for k_a, central volume of distribution, volume distribution of peripheral compartment, intercompartmental clearance and their variabilities were tested as structural models. Interindividual variability was evaluated by an exponential model and the additive, the proportional, and the slope-intercept error models were tested for residual variability. The validity of the model was tested by the internal validation techniques.

Results: The two-compartment model with use of priors and slope-intercept residual error was selected as structural modelbased on the favorable AIC and BIC values. According to the final model typical value of sirolimus apparent clearance (CL/F) was 12.2 L/h. It was significantly influenced by age and the liver function parameter aspartate aminotransferase (AST). CL/F was found to decrease with age. According to the developed population pharmacokinetic model, sirolimus CL/F was decreased approximately 37% (95% CI 26, 48%) in patients with AST greater than 37 IU/l. The prediction- and variability-corrected visual predictive check and numerical predictive check confirmed satisfactory prediction of developed model.

Conclusions: The population modeling of TDM data with use of informative priors allowed partial explanation of the interindividual variability in CL/F.According to the developed model patients with compromised liver function expressed via AST values require careful monitoring and dosing adjustments.

References:

[1] Dansirikul C, Morris RG, Tett SE, Duffull SB. A Bayesian approach for population pharmacokinetic modelling of sirolimus. Br J Clin Pharmacol. 2006; 62: 420 - 434.

[2] Jiao Z, Shi XJ, Li ZD, Zhong MK. Population pharmacokinetics of sirolimus in de novo Chinese adult renal transplant patients. Br J Clin Pharmacol. 2009; 68: 47 - 60.

I-25: *Ignacio Gonzalez* Assessment of in vitro dissolution specifications based on an IVIVC and in vivo bioequivalence criteria

I González-García (1) ,V Mangas-Sanjuan (2), M Merino-Sanjuán (3), A García-Arieta (4), IF Trocóniz (2), M Bermejo (5)

(1) Pharma Mar, Madrid, Spain; (2) Pharmacometrics and Systems Pharmacology. Pharmacy and Pharmaceutical Technology Department. University of Navarra; (3) Pharmacy and Pharmaceutical Technology Department. University of Valencia; (4) Head of Service on Pharmacokinetics and Generic Medicines, Division of Pharmacology and Clinical Evaluation, Department of Human Use Medicines, Spanish Agency for Medicines and Health Care Products; (5) Pharmacy and Pharmaceutical Technology Area. Miguel Hernandez University

Objectives: The main objective of this work is to assess the influence of *in vitro* inter-batch and *in vivo* inter-individual variability for the establishment of dissolution specifications based on an *in vitro-in vivo* correlation (IVIVC) and the *in vivo* bioequivalence (BE) standards. The final aim is to assess whether the *in vitro* specifications to ensure BE should be based on average dissolution data and average *in vivo* profiles or should incorporate *in vitro* and *in vivo* variability.

Methods: Dissolution profiles with three different (slow, medium and fast) release rates (first-order kinetics) were simulated and their corresponding *in vivo* profiles were obtained through a link model implemented in NONMEM assuming a linear level A IVIVC [1]. The medium release rate formulation was taken as reference. Then two test formulations were simulated; Test 1 with a very similar dissolution profile (*i.e.*, BE based on the IVIVC) and Test 2 was a borderline formulation with f_2 similarity factor value close to 50. Four scenarios of variability were considered (high (30%) or low (15%) for *in vitro* and *in vivo*). Residual variability was set at 5%. All variability terms were described with exponential models. *In vivo* profiles obtained through the IVIVC were analyzed to obtain Cmax and AUC ratios and their 90% confidence intervals (CI). All simulated scenarios (n=1000) were performed using non-linear mixed-effects modelling implemented in NONMEM 7.3[1]. For graphical and statistical analysis, the R (v.3.2.2) software and RStudio (v.0.99) were used.

Results: For both test formulations BE was concluded based on the average *in vivo* profiles which were included within BE limits (0.8 to 1.25) in all the variability scenarios. Nevertheless, when variability was accounted for and the BE analysis was based on the 90% CI, the borderline test formulation failed to show BE in the high variability scenarios

Conclusions: These results point out the relevance of taking into account *in vitro* and *in vivo* variability for setting dissolution specifications based on a validated IVIVC. Formulations with high inter-batch variability (even within quality control limits) could have average *in vivo* profiles within BE limits but fail under the 90% CI approach.

References:

[1] Gaynor C, Dunne A, Costello C, Davis J. A population approach to in vitro–in vivo correlation modelling for compounds with nonlinear kinetics. J Pharmacokinet Pharmacodyn 2011;38: 317–32.

I-26: *Verena Gotta* Characterizing age-dependency of cytokine levels in healthy children

Verena Gotta (1), Marie-Luise Summerer (1), Sven Wellman (1), Andrea Zelmer (1), Christian Schindler (2) and Nicole Ritz (1)
(1) University of Basel Children's Hospital, Basel, Switzerland, (2) Swiss Tropical and Public Health Institute in Basel, Switzerland

Objectives: To characterize the age-dependency and normal ranges of eight cytokines in healthy children (IL-1ra, IL-2, IL-4, IL-6, IL-10, IP-10, IFN-γ and TNF-α), as well as the age-dependency of cytokine release following antigen stimulation *ex vivo*.

Methods: Healthy children aged 0-12 years undergoing elective/diagnostic procedures were eligible for inclusion. Whole blood was stimulated *in vitro* for 24 hours using Staphylococcus enterotoxin B, Phytohaemagglutinin or *Candida albicans* or left unstimulated, and cytokine concentrations were measured using a Luminex bead-based multiplex assay (precision: 2-19%, lower limit of quantification LLOQ=3.2 pg/mL). Data was analyzed by censored mixed effect regression analysis in NONMEM version 7.3 to evaluate linear and non-linear relationships of cytokine levels with age. Between-subject variability (BSV) was assumed to be log-normally distributed, unless variability-misspecification was evident in visual predictive check diagnostic. Only details of unstimulated cytokine data is presented here.

Results: A total of 271 children were included (median age 5.2 years, IQR 3.4-7.8; 74% male). Generally, unstimulated samples were negatively correlated with age, while stimulated samples were mostly positively correlated with age. A high proportion of unstimulated samples was <LLOQ (IL-2, IL-4, IL-10, IL-6: ≥70%, IFN-γ: 39%, IL-1ra: 7%, TNF-α: 6%, IP-10: 3%). TNF-α showed the strongest age-dependency, with an exponential decline of 30%/year ('half-life' $t_{1/2}$=2.3 years, baseline=19 pg/mL, lower asymptote=7 pg/mL, p<0.001). IL-1ra decreased by 7%/year ($t_{1/2}$=9 years, p=0.008), while a lower asymptote could not be quantified. BSV was large (74% to 240%), and was only to a small part (3-7%) explained by age. An age-dependency could not be quantified for the other cytokines, but was suggested by increasing proportions of data below the LLOQ in older age groups. Residual unexplained variability was 19%.

Conclusions: In healthy children unstimulated levels of TNF-α and IL-1ra decrease during the first 12 years of life. The other cytokines did not show a clear association with age, but the detection of such an association may have been impeded by the large proportion of data below LLOQ. The importance of age-dependent levels of these two important pro-inflammatory and anti-inflammatory cytokines need to be further investigated. It may be relevant for choosing the optimal dose of immune-modulating drugs in pediatric patients.

I-27: *Gopichand Gottipati* Item Response Modeling to Leverage Data from Historical Parkinson's Disease Trials while Integrating Data from a Newer Version of the Clinical Endpoint

Gopichand Gottipati(1), Alienor C. Berges(2), Shuying Yang(2), Chao Chen(2), Mats O. Karlsson(1), Elodie L. Plan(1)
(1) Dept of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (2) GlaxoSmithKline, Harlow, UK

Objectives: Unified Parkinson's Disease Rating Scale (UPDRS) has been used for assessing disease severity in Parkinson's Disease (PD) trials for several decades. More recently, a Movement Disorder Society sponsored revision (MDS-UPDRS) had been proposed [1]. The objective of this work was to develop a framework to leverage historical data through the application of Item Response Theory (IRT) methodology.

Methods: An IRT model with three (hidden) latent variables [2], was previously developed using the MDS–UPDRS data of the De Novo PD cohort from the Parkinson's Progression Markers Initiative database [3]. This model was adapted to describe the baseline UPDRS data from two clinical trials, one in subjects with early PD [4] and the other in subjects with advanced PD [5]. Assuming that the same underlying latent variables reflected the disease severity, items of the original version were mapped to those of the new version. For 41 shared items the parameters were fixed except for aspects related to minor differences in item categorization. For the remaining 14 items, new item parameters were estimated. Modeling was performed using NONMEM7.3 and evaluated with PsN and R.

Results: The parameters reflecting differences in the shared items between scales or characterization of new item parameters, were estimated successfully. The mean (and variance) of the latent variables for the patient reported items, non-dexterous items, dexterous items according to the affected side were 0.472 (0.771), 0.225 (1.31), 0.333 (0.743) in the early PD patients respectively and 1.12 (1.70), 2.10 (2.21), 0.683 (1.48) in the advanced PD patients respectively. EBE and simulation based diagnostics indicated that mapping between the two versions was better for early PD subjects (close to De Novo cohort of PPMI) than advanced PD subjects. Background (L-dopa) therapy in one of the two studies seemed to induce differences in some item characteristic curves, which could be described as a covariate effect.

Conclusions: The two versions of the main clinical endpoint in PD trials, UPDRS and MDS-UPDRS, can be integrated together in a unique framework using IRT methodology. This can facilitate improved utilization of the data by integrating data from diverse sources, including different versions of the endpoint (as long as they are mapped to the same underlying latent variables), and potentially lead to better characterization of disease progression and drug effects in PD.

References:
[1] Goetz C., Tilley B, Shaftman S, Stebbins G, Fahn S, Martinez M, Werner Poewe et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Movement Disorders 2008; 23(15): 2129-2170.
[2] Gottipati G, Karlsson MO, Plan EL., Modeling of a Composite Score in Parkinson's Disease using Item Response Theory. PAGE 24 (2015) Abstract 3596 [www.page-meeting.org/?abstract=3596]
[3] The Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org
[4] Stocchi F, Hersh BP, Scott BL, Nausieda PA, Giorgi L; Ease-PD Monotherapy Study Investigators.

Ropinirole 24-hour prolonged release and ropinirole immediate release in early Parkinson's disease: a randomized, double-blind, non-inferiority crossover study. Curr Med Res Opin. 2008; 24(10):2883-95
[5] Pahwa R, Stacy MA, Factor SA, Lyons KE, Stocchi F, Hersh BP, Elmer LW, Truong DD, Earl NL; EASE-PD Adjunct Study Investigators. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology. 2007; 68(14):1108-15.

I-28: *Sebastiaan Goulooze* Monte-Carlo simulations of the clinical benefits and feasibility of therapeutic drug monitoring trials of sunitinib in patients with gastrointestinal stromal tumours.

Sebastiaan C. Goulooze (1,2) and Jennifer H. Martin (2).
(1) Division of Pharmacology, Leiden Academic Centre for Human Drug Research, Leiden, The Netherlands, (2) School of Medicine and Public Health, University of Newcastle, NSW, Australia.

Objectives: Due to large interpatient variability, therapeutic drug monitoring (TDM) is being considered to individualise cancer treatment with tyrosine kinase inhibitors such as sunitinib[1]. However it remains unclear what impact sunitinib TDM could have on the clinical outcome of eligible patients. The aim of this study was to: (a) estimate the expected improvement in time to tumour progression (TTP) in patients with gastrointestinal stromal tumours (GIST) treated with an initial dose of 37.5 mg/day sunitinib, and (b) assess feasibility of a sunitinib TDM trial by estimating the number of subjects required for sufficient statistical power.

Methods: Simulations were performed in R, based on published models of the pharmacokinetics and pharmacodynamics of sunitinib[2,3]. The dynamics of the impact of drug exposure change on the TTP hazard rate are unknown. Therefore two scenarios were simulated: an optimistic scenario with an immediate impact and a conservative scenario with a very gradual impact. Dose-limiting toxicity (67%) and patient drop-out (biweekly rate of 0.2%) were included in the simulations used to estimate required study size.

Results: Two rounds of TDM reduced the percentage of patients below target exposure levels from 52% to 16%.For patients with an initial exposure below the target, median TTP was estimated at 216 days with a fixed dosing regimen. TDM increased the TTP of eligible patients to 249 days (+15%) and 283 (+31%) days in the 'gradual' and 'immediate' impact scenario. However, an estimated 1600 (immediate impact) or 3800 (gradual impact) subjects are required for a sunitinib TDM trial to be powered to detect a significant impact on TTP.

Conclusions: Although clinical data on the impact of sunitinib TDM is lacking, the simulations suggest a clinically relevant increase for eligible patients. However, considering the fact that GIST is a rare cancer (and sunitinib not its first line treatment), the number of subjects required for a TDM trial are likely prohibitively high. Pharmacometric modelling and simulation might support evidence-based TDM practices when prospective TDM trials are not feasible due to low number of eligible patients.

References:
[1] Lankheet NA, Kloth JS, Gadellaa-van Hooijdonk CG, Cirkel GA, Mathijssen RH, Lolkema MP, Schellens JH, Voest EE, Sleijfer S, de Jonge MJ, Haanen JB, Beijnen JH, Huitema AD, Steeghs N. Pharmacokinetically guided sunitinib dosing: a feasibility study in patients with advanced solid tumours. Br J Cancer (2014) 110(10):2441-2449.
[2] Yu H, Steeghs N, Kloth JS, de Wit D, van Hasselt JG, van Erp NP, Beijnen JH, Schellens JH, Mathijssen RH, Huitema AD. Integrated semi-physiological pharmacokinetic model for both sunitinib and its active metabolite SU12662. Br J Clin Pharmacol (2015) 79(5):809-819.
[3] Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemother Pharmacol (2010) 66(2):357-371.

I-29: *Sylvain Goutelle* A nonparametric, multiple-model approach to optimize initial dosing and attainment of a target exposure interval: application to busulfan in pediatrics

Michaël Philippe (1,2), Michael Neely (3), Yves Bertrand (1), Nathalie Bleyzac (1,2), Sylvain Goutelle (2,4,5)
(1) Institute of Pediatric Hematology and Oncology, Lyon, France, (2) Laboratoire de Biométrie et Biologie Evolutive, UMR CNRS 5558, Université Lyon 1, Villeurbanne, France , (3) Laboratory of Applied Pharmacokinetics and Bioinformatics, Division of Pediatric Infectious Diseases, University of Southern California Children's Hospital Los Angeles, Los Angeles, USA, (4) Université Lyon 1, ISPB - Faculté de Pharmacie de Lyon, Lyon, France, (5) Service Pharmaceutique, Groupement Hospitalier de Gériatrie, Hospices Civils de Lyon, Lyon, France

Objectives: The traditional approach for model-based initial dosing is based on the use of a single vector of typical population parameters for targeting a specific exposure [1]. This approach is theoretically ill-suited for targeting a range of exposure [2]. The objective of this work was to develop a general approach for optimal targeting of a drug exposure interval.

Methods: We used the nonparametric population pharmacokinetic (PK) model of IV busulfan (Bu) from Neely et al [3] to estimate the individual PK parameters of 163 bone marrow transplanted children (age= 6.1 ± 5.0 years old, IBW= 20.9 ± 13.9 kg) treated by IV Bu in Lyon (France). Then, an array of 151 doses of Bu ranging from 0.5 to 2 mg/kg was simulated a priori in each patient. For each dose, 29 possible Bu plasma concentration profiles, corresponding to the nonparametric prior, each associated with a probability, were obtained. The multiple-model (MM) -based, optimal dose was identified as that maximizing the a priori probability of achieving the Bu target AUC. Two AUC targets were considered: 900 – 1500 (conventional) or < 1500 µM.min^{-1}. Finally, the MM optimal dose was individually simulated in each patient. We compared the ability of this method to achieve the target exposure interval with that of three other traditional model-based methods [4,5,6], during a 4-day q.i.d. regimen of IV Bu.The Matlab software was used for all calculations.

Results: When targeting Bu conventional AUC range (900 – 1500 µM.min^{-1}), the MM-dosing approach provided better attainment of than the best of the three other methods after one Bu dose, (82.2% versus 41.6%, *p<0.005*), two doses (79.1% versus 65.0%, *p<0.005*) and at the end of therapy, i.e. 16 doses (80.4% versus 76.7%, *p<0.42*). The approach provided a balanced distribution between under- (10.4%) and overexposure (9.2%), while other approaches showed higher rates of underexposure (≥ 19%). When targeting an AUC < 1500 µM.min, the MM approach was successful in minimizing overexposure as 0% of children showed simulated AUC > 1500 µM.min^{-1}; while this percentage ranged from 0.6% to 4.3% for the other approaches.

Conclusions: A MM approach has been designed to optimize the targeting of an exposure interval. When applied to Bu in children, it outperformed the traditional model-based dosing approach, with earlier and better achievement of Bu target AUC. The approach can be applied for optimal dosing of many drugs, when the target objective is an interval.

References:

[1] Holford NH. Target concentration intervention: beyond Y2K. Br. J. Clin. Pharmacol. 2001;52 Suppl 1:55S – 59S
[2] D'Argenio DZ, Rodman JH. Targeting the systemic exposure of teniposide in the population and the

individual using a stochastic therapeutic objective. J. Pharmacokinet. Biopharm. 1993;21:223–51.
[3] Neely M , et al. Accurately achieving target busulfan exposure in children and adolescents with very limited sampling and the BestDose software. *To be published in Therapeutic Drug Monitoring 2016*
[4] Nguyen L, et al. I.V. busulfan in pediatrics: a novel dosing to improve safety/efficacy for hematopoietic progenitor cell transplantation recipients. Bone Marrow Transplant. 2004;33:979–87.
[5] Paci A, et al. Pharmacokinetic behavior and appraisal of intravenous busulfan dosing in infants and older children: the results of a population pharmacokinetic study from a large pediatric cohort undergoing hematopoietic stem-cell transplantation. Ther. Drug Monit. 2012;34:198–208.
[6] McCune JS, et al. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin. Cancer Res. 2014;20:754–63

I-30: *Joachim Grevel* Exposure-response analysis for efficacy and safety of sorafenib in patients with differentiated thyroid carcinoma (DTC)

Joachim Grevel (1) Garrit Jentsch (1), Rupert Austin (1), John Lettieri (2), Bart Ploeger (3), Ping Ji (2), Gerold Meinhardt (2), and Carol Peña (2)
(1) BAST Inc Ltd., UK, (2) Bayer Healthcare Pharmaceuticals, US, (3) Bayer Pharma AG, Germany

Objectives: To develop a time-to-event (TTE) model for adverse events (AE) and clinical response (progression-free survival, PFS) in relation to sorafenib dose rate (DR) and plasma exposure in DTC. To simulate the benefit and risk of various starting doses and dose reduction schedules.

Methods: PFS, AE and PK data from 206 patients randomised to 400 mg sorafenib BID and 207 placebo treated patients from a Phase 3 DTC trial (DECISION; NCT00984282) were used. Sparse PK data were converted into individual AUCs by an existing popPK model [1]. DR and AUC(0-12) were tested as covariates (average until the event or time-varying) in a TTE analysis (using NONMEM) of PFS (centrally assessed) and 5 AEs (any first event of Grade ≥3, any first event of Grade ≥4, hand-foot skin reaction (HFS) Grade 3, hypertension Grade ≥3, diarrhoea Grade ≥2). The parametric hazard models with covariate influences were used to simulate events for starting doses of 800, 600, or 400 mg/day, and for 2 cycles of 800 mg/day followed by either 600 mg/day or 400 mg/day either maintained or for 2 cycles followed by up-titration.

Results: The average AUC(0-12) had the strongest influence on PFS compared to the other dose/exposure covariates which were less significant. The hazard ratio for 800 mg/day versus 600 mg/day and 400 mg/day was 0.814 and 0.638, respectively. The influence of average DR on the hazard of any Grade ≥3 AEs and on HFS was stronger than that of the time-varying DR. The AUC exposure metrics had no significant influence. For diarrhoea, time-varying DR had the strongest influence. For hypertension and Grade ≥4 AEs, no covariates were significant. Benefit/risk was assessed graphically for DR ranging from 800 mg/day to 0 mg/day (placebo) as the fraction of patients with AEs Grade ≥3 and with tumour progression over a 400 day treatment period.

Conclusions: All simulations emphasised the importance of high DR or exposure early in treatment. All dose reduction schemes starting with 2 cycles of 800 mg/day of sorafenib had similar benefit and risk. Lower starting doses than 800 mg/day could not be justified as less AEs were offset by reduced efficacy.

References:

[1] Prins NH, Grevel J , Mitchell D, Lettieri J,4 Ploeger B, Peña C. Population pharmacokinetics of sorafenib: a meta-analysis of patients with hepatocellular carcinoma, renal cell carcinoma, and differentiated thyroid carcinoma. J Pharmacokin Pharmacodyn (2014) 41:S23.

I-31: *Monia Guidi* Population pharmacokinetic analysis of the IAPs antagonist Debio 1143 and its major metabolite in oncologic patients

M. Guidi (1) (2), C. Csajka (1) (2), A. Haouala (3), A. Ménétrey (3) and E. Rouits (3)
(1) School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Geneva, Switzerland; (2) Division of Clinical Pharmacology, Department of Laboratories, University Hospital Lausanne, Lausanne, Switzerland; (3) Debiopharm International, Lausanne, Switzerland.

Objectives: Debio 1143 (D-1143) is an orally administered antagonist of Inhibitors of Apoptosis Proteins (IAPs) currently in clinical development for cancer therapy. D-1143 and its major metabolite (D-1143-M) pharmacokinetics (PK) was investigated in three Phase I clinical studies as a single agent, in combination with cytarabine/daunorubicin (Cyt/Daun) and with carboplatin/paclitaxel (Carbo/Pac) [1-3]. The aim of the present study was to characterize D-1143 and D-1143-M PK and their variability in relation to potential influencing covariates and to drug/metabolite interaction.

Methods: Full PK profiles of D-1143 and D-1143-M in two occasions and several trough concentrations were available for the PK analysis (NONMEM®). Multi-compartment models with linear elimination and a variety of absorption models were compared to depict D-1143 PK. D-1143-M concentrations were described by assuming linear metabolism from D-1143 and by adding one or two compartments. Drug/metabolite interaction was evaluated through different inhibition models. Demographic characteristics, coadministered chemotherapy agents and biochemical parameters were tested as covariates.

Results: 94 oncologic patients provided 1717 D-1143 and 888 D-1143-M concentrations. D-1143 PK was best characterized by a two compartment model with sequential zero- and first-order absorption with one additional compartment for D-1143-M disposition. Assignment of distinct bioavailabilities to full profile occasions and trough concentrations allowed describing the non-linearity in drug PK. An important interindividual variability (IIV) was associated with the majority of the PK parameters. The D-1143/D-1143-M mutual interaction was best captured using AUC_D and AUC_M as covariates on metabolite (CL_M) and drug clearance (CL_D), respectively. A decrease of 22% in CL_M and 13% in CL_D was observed doubling AUC_D and AUC_M, respectively. Coadministration of Carbo/Pac lowered CL_D by 35% compared to participants receiving Debio 1143 alone or in combination with Cyt/Daun. These covariates explained all together the totality of CL_M IIV and 28% of CL_D IIV.

Conclusions: D-1143 PK is characterized by non-linear kinetics. The large variability associated with drug and metabolite PK remains unexplained, despite the inclusion of D-1143/D-1143-M mutual interaction and of Carbo/Pac coadministration as covariates. The Carbo/Pac effect, however, is under investigation since it could not be disentangle from other study specificities.

References:
[1] Ascenta Therapuetics Inc., AT-406-CS-001: A phase I, open label, multi-center, dose escalation study of the safety, tolerability, pharmacodynamic and pharmacokinetic properties of orally administered AT-406 in patients with advanced solid tumors and lymphomas. 2013.
[2] Ascenta Therapuetics Inc., AT-406-CS-002: Phase I dose escalation study of the safety, tolerability, pharmacokinetics, and pharmacodynamic properties of oral AT-406 in combination with daunorubicin and cytarabine in patients with poor-risk, acute myelogenous leukemia (AML). 2013.
[3] Debiopharm International, Debio 1143: Investigator's Drug Brochure. 2013.

I-32: *Elham Haem* Adjusted adaptive lasso for covariate model building in nonlinear mixed effects models

Elham Haem (1,2), Kajsa Harling (2), Seyyed Mohammad Taghi Ayatollahi (1) Najaf Zare(1) and Mats O. Karlsson (2)
(1) Department of Biostatistics, Shiraz University of Medical Sciences school of Medicine, Shiraz, Iran,(2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.

Objectives: This study aimed to propose and implement a new version of lasso, Adjusted Adaptive Lasso [1], for non-linear mixed effects models. The new method takes into account the standard errors of the maximum likelihood coefficient estimators for covariate estimation and selection in population pharmacokinetics when there is multicollinearity. We also compared mean absolute prediction error and error of estimated coefficient of covariates with Adaptive Lasso [2] and simple Lasso [3].

Methods: Data sets were simulated with 20 40, 80 or 120 individuals, in which each subject had three PK observations, from a one compartment i.v.bolus model. Ten covariates were created by sampling from a multivariate normal distribution with no, low (0.2), moderate (0.5) and high (0.7) correlation among them. Four true covariates with different magnitudes influenced clearance. Adjusted Adaptive Lasso, Adaptive Lasso and Lasso were implemented using PsN and NONMEM 7.3. The methods were compared to each other in terms of mean absolute prediction error and error of estimated coefficient of covariates in 16 scenarios with different dataset sizes and distinct values of correlation among covariates. All simulation scenarios were replicated 100 times.

Results: Simulation results showed that Adjusted Adaptive Lasso had advantage in terms of both mean absolute prediction error and error of estimated coefficient of covariates comparing with other methods when data sets were small and in particular for no, small and moderate correlation among covariates. However, the benefit was negligible for large data sets.

Conclusions: Adjusted Adaptive Lasso outperformed Adaptive Lasso and simple Lasso in obtaining a predictive covariate model on small data sets.

References:

[1] Algamal Z. Y & Lee M. H . Adjusted adaptive lasso in high-dimensional poisson regression model. Modern Applied Science (2015), 9(4):170–177.
[2] Zou H. The adaptive lasso and its oracle properties. Journal of the American Statistical Association (2006), 101:1418–1429.
[3] Ribbing J, Nyberg J, Caster O & Jonsson E.N. The lasso-a novel method for predictive covariate model building in nonlinear mixed effects models. J Pharmacokin Pharmacodyn (2007). 34 (4):485–517 .

I-34: *Janelle Hajjar* Modeling Duchenne muscular dystrophy disease progression as assessed by the 6-minute walk test

Janelle Hajjar (1,2), CJ Godfrey (3), Jeannine Fisher (3), Marc R. Gastonguay (1,2,3)
(1) University of Connecticut, Storrs, CT, USA, (2) Metrum Institute, Tariffville, CT, USA (3) Metrum Research Group, LLC, Tariffville, CT, USA

Objectives: To build a disease progression model of Duchenne muscular dystrophy (DMD), a rare disease, given public source 6-minute walk test (6MWT) data.

Methods: PubMed (www.pubmed.gov) was searched using PRISMA 2009 Standards [1] to obtain all publically available natural history or placebo data of the 6MWT in boys with DMD. Individual level 6MWT data of boys under 18 years of age were included in the analysis. Nonlinear mixed effects models were implemented with NONMEM® Version 7.3. A baseline model was fit with initial estimates based on summary statistics of literature population values. The final estimates of the baseline model were fixed in the fitting of a longitudinal disease progression model.

Results: Public data were available for 254 boys from 5 unique studies [2-6]. 4 boys were excluded due to inability to capture data. 129 boys had baseline data only. Baseline 6MWT across the population sample was described as an exponential function of age, with a sigmoid Emax maturational effect and exponential individual random effect. The final longitudinal model included baseline plus a linear slope with respect to elapsed time and an additive individual random effect. Observed baseline 6MWT (BL0) was a predictor of slope, dichotomized at BL0 <= 350 meters or > 350 meters. The standard deviation of the residual error was fixed to the literature value of 4 meters [5]. The point estimates and standard errors (SEs) of the slopes for <=350 vs >350 BL0 were -65.9 (20.2) meters/year and -24.8 (1.60e3) meters/year, respectively. The variances of the interindividual random effects for baseline and slope were 0.0596 (0.00377) and 9250 (1050), respectively. Inclusion of steroid use and study type (observational or trial setting) did not improve goodness of fit.

Conclusions: This analysis quantified the large variability in the longitudinal progression of DMD as measured by the 6MWT. Even after partitioning progression slopes for baseline 6MWT, considerable unexplained variability remained. The sigmoid component of the baseline model captured the maturational trend in boys ages 4-7 years old, when disease progression is often masked by childhood growth. The impact of additional covariates such as genetic information, medication history, or age of diagnosis is unknown, due to limitations in the public data sources. Future prospective analyses should consider evaluating these effects.

References:

[1] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
[2] Brehm M-A, Kempen JCE, van der Kooi AJ, de Groot IJM, van den Bergen JC, etal. (2014) Age-Related Longitudinal Changes in Metabolic Energy Expenditure during Walking in Boys with Duchenne Muscular Dystrophy. PLoS ONE 9(12): e115200. doi:10.1371/journal.pone. 0115200
[3] Goemans N, van den Hauwe M, Wilson R, van Impe A, et al. (2013) Ambulatory capacity and disease progression as measured by the 6-minute-walk-distance in Duchenne muscular dystrophy subjects on daily corticosteroids. Neuromuscul Disord. 23(8) 618-623. doi: 10.1016/j.nmd.2013.05.006

[4] Mazzone E, Martinello D, Berardinelli A, Messina S, et al (2010) North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord. 20(11) 712-716. doi: 10.1016/j.nmd.2010.06.014
[5] McDonald CM, Henricson EK, Han JJ, Abresch RT, et al. (2010) The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve 41 500–510. doi: 10.1002/mus.21544
[6] Mcdonald CM, Henricson EK, Abresch RT, Florence JM, et al. (2013) The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve 48 343–356. doi: 10.1002/mus.23902

I-35: *Nayoung Han* Dose estimation based on population pharmacokinetic/pharmacogenetic modeling for enteric-coated mycophenolate sodium in kidney transplant recipients

Nayoung Han(1), Hwi-yeol Yun(1), In-Wha Kim(2), Yoon Jung Oh(3), Yon Su Kim(4), Jung Eben(1), Yoo younghoon(1), Jung Mi Oh(2)*

(1) College of Pharmacy, Chungnam National University, Korea; (2) College of Pharmacy, Seoul National University, Korea; (3) Department of Internal Medicine, Cheju Halla General Hospital, Korea; (4) Department of International Medicine, College of Medicine, Seoul National University, Korea

Objectives: Enteric-coated mycophenolate sodium (EC-MPS) is effective and safe in preventing rejection after transplantation and is mainly transported by ABCs and OATPs and metabolized by UGTs. The genetic polymorphisms affect the inter-individual variation in drug disposition and elimination. The aims of this study were to develop a population pharmacokinetic (PK) model and to evaluate the influence of genetic and clinical factors on the PK of mycophenolic acid (MPA) in Korean renal transplant recipients.

Methods: Population analysis of EC-MPS was performed using non-linear mixed effects modeling (NONMEM). After clinical and genetic factors were evaluated using a stepwise covariate method (SCM), we selected clinically relevant covariates considering covariate effects and covariates were identified by using bootstrap analyses of the SCM. The final model was validated by bootstrap and visual predictive check. At last, we performed the model-based simulations in order to explore an optimal dose to achieve target area under the curve (AUC) in hypothetical scenarios.

Results: From 166 plasma concentrations in 34 patients, a time-lagged two-compartment with a flip-flop model best describes the PK of MPA. The covariate analysis identified lower creatinine clearance (CLcr) and *SLCO1B1* variant genotype were correlated with lower MPA clearance, on the contrary, *UGT1A9* variant had decreased distribution of MPA, contributing to lower absorption. When considering to *UGT1A9*, *SLCO1B1* genotypes, and renal function, the new recommended dose of 540 mg twice daily resulted in a higher success of achieving the target $AUC_{(0\text{-}12h)}$ in the 30-60 mg.h/L.

Conclusions: In conclusion, CLcr, *UGT1A9* and *SLCO1B1* genotypes seem to be promising parameters to predict the pharmacokinetics with flip-flop phenomenon of EC-MPS in transplant recipient having stable renal function. This model on clinical practice may help prevent overexposure and achieve a proper AUC in the Korean population.

I-36: *Nina Hanke* Physiologically-based Pharmacokinetic Modeling of Rifampin Drug-Drug Interactions with Midazolam and Digoxin

Nina Hanke (1), Sebastian Frechen (2), Hannah Britz (1), Daniel Moj (1), Tobias Kanacher (2), Thomas Eissing (2), Thomas Wendl (2) and Thorsten Lehr (1)
(1) Clinical Pharmacy, Saarland University, Saarbruecken, Germany, (2) Bayer Technology Services GmbH, Systems Pharmacology CV, Leverkusen, Germany

Objectives: Physiologically-based pharmacokinetic (PBPK) modeling is a powerful tool to explore and quantitatively predict the magnitude of drug-drug interactions (DDIs) and may even offer an alternative to dedicated clinical studies. Rifampin is an established potent inducer of multiple drug metabolizing enzymes and transporters. Therefore, the FDA recommends rifampin as inducer for the assessment of the DDI potential of investigational new drugs[1]. Our objective was to build and evaluate PBPK models of rifampin and digoxin to predict the DDIs of rifampin with midazolam (CYP3A4 substrate) and digoxin (P-gp substrate).

Methods: PBPK models of rifampin and digoxin were built in PK-Sim® modeling software (Version 6.0.3)[2]. Drug-dependent parameters as well as plasma-, urine- and bile concentration-time profiles of various clinical studies (broad dosing range, intravenous (iv) and oral (po) application, single- and multiple-dosing) were obtained from literature and used to establish models accurately describing and predicting observed clinical study data. Processes mediating the induction and simultaneous competitive inhibition of CYP3A4 and P-gp were integrated into the rifampin model[3-6]. Finally, the rifampin model was coupled to the digoxin model and a previously developed midazolam model[7].

Results: Our new rifampin model applies transport processes (P-gp and OATP1B1), metabolism by arylacetamide deacetylase (AADAC) and glomerular filtration. Auto-induction of P-gp and AADAC by rifampin was taken into account. The newly developed digoxin model features P-gp transport in various organs including gut, liver and kidney. Implementation of target binding (Na^+/K^+-ATPase) was crucial to accurately describe published plasma concentrations after iv and po administration of digoxin. Simulation of the DDIs with the coupled models generates midazolam and digoxin plasma concentration-time profiles during rifampin treatment that are in good agreement with observed data. Predicted AUC ratios (AUC with rifampin /AUC without) show an acceptable fold bias of 1.39 (geometric mean fold absolute deviation, range 1.00-1.96, N=5) for midazolam and of 1.04 (range 1.02-1.07, N=4) for digoxin.

Conclusion: We provide PBPK models of rifampin and digoxin as tools for the drug development process to evaluate the DDI potential of investigational drugs that are CYP3A4 or P-gp substrates (coupling to the rifampin model) or P-gp inducers or inhibitors (coupling to the digoxin model).

References: [1] Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. 2012. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER).
[2] Eissing T, Kuepfer L, Becker C, Block M, Coboeken K, Gaub T, Goerlitz L, Jaeger J, Loosen R, Ludewig B, Meyer M, Niederalt C, Sevestre M, Siegmund H, Solodenko J, Thelen K, Telle U, Weiss W, Wendl T, Willmann S, Lippert J. A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front Physiol (2011) 2: 4.
[3] Templeton IE, Houston JB, Galetin A. Predictive utility of in vitro rifampin induction data generated in

fresh and cryopreserved human hepatocytes, Fa2N-4, and HepaRG cells. Drug Metab Dispos (2011) 39(10): 1921-9.
[4] Greiner B, Eichelbaum M, Fritz P, Kreichgauer HP, von Richter O, Zundler J, Kroemer HK. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest (1999) 104(2): 147-53.
[5] Kajosaari LI, Laitila J, Neuvonen PJ, Backman JT. Metabolism of repaglinide by CYP2C8 and CYP3A4 in vitro: effect of fibrates and rifampicin. Basic Clin Pharmacol Toxicol (2005) 97(4): 249-56.
[6] Reitman ML, Chu X, Cai X, Yabut J, Venkatasubramanian R, Zajic S, Stone JA, Ding Y, Witter R, Gibson C, Roupe K, Evers R, Wagner JA, Stoch A. Rifampin's acute inhibitory and chronic inductive drug interactions: experimental and model-based approaches to drug-drug interaction trial design. Clin Pharmacol Ther (2011) 89(2): 234-42.
[7] Wendl T, Frechen S, Teutonico D, Hermes HE, Pilari S, Eissing T. A whole-body physiologically-based pharmacokinetic (PBPK) model for itraconazole and its metabolite to predict dynamic drug-drug-interactions. PAGE 24 (2015) Abstr 3517.

I-37: *Fangran Hao* Pharmacokinetic-pharmacodynamic modeling of the anti-tumor effect of sunitinib combined with dopamine in the human non-small cell lung cancer xenograft

Fangran Hao, Siyuan Wang, Wei Lu, Tianyan Zhou
Department of Pharmaceutics, School of Pharmaceutical Sciences, Peking University, Beijing, China

Objectives: Lung cancer is the most lethal form of cancer in the world (1). Sunitinib is a promising multi-targeted receptor tyrosine kinase (RTK) inhibitor with activity against vascular endothelial growth factor receptors (VEGFR-1 and -2), platelet-derived growth factor receptors (PDGFR-α and -β), stem-cell factor receptor (KIT), etc (2). However, drug resistance (3) has limited its clinical application. In order to investigate the possibility of reversion of multidrug resistance in lung adenocarcinoma cell line A549, the study attempted to explore the anti-tumor synergistic effect of dopamine on sunitinib in a human non-small lung cancer xenograft, as well as to develop the PK/PD models of this combination therapy.

Methods: Female BALB/c nude mice were implanted with the human NSCLC cell line A549. In the monotherapy group, the animals were given sunitinib (10 or 20mg/kg) by oral administration daily or two different doses of dopamine (1 or 2mg/kg) by tail intravenous injection every three days; in the combination therapy group, 10mg/kg sunitinib was given concurrently with 1mg/kg dopamine and 20mg/kg sunitinib was given concurrently with 2mg/kg dopamine. Pharmacokinetics of sunitinib was determined in our previous study (4). The natural growth curves of A549 cells xenografts could be well fitted with an exponential phase followed by a linear growth phase. A transit compartment model was introduced to describe the cell-killing effect induced by sunitinib. The influence of dopamine on the model was reflected via an on/off effect.

Results: The pharmacokinetics of sunitinib and its active metabolite SU12662 was described by a two-compartment model with first-order extravascular absorption kinetics. Evident synergism was observed when sunitinib and dopamine were given concurrently, as the combination therapy exhibited remarkable lower tumor burden than the monotherapy. A shape factor was put on the apoptosis rate constant to explain the enhanced antitumor effects, which was estimated as 0.003. The transit rate constant obtained from the model was estimated as 0.519 and the first order apoptosis rate constant was 0.126. The good predictive function was found by visual predictive check.

Conclusion: The pharmacokinetic/pharmacodynamics model built in this study contributes to understanding the synergistic effect of dopamine on sunitinib. Furthermore, it is helpful in predicting the efficacy of dopamine when combined with other chemotherapeutic drugs.
References:

References:
[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.
[2] Li M, Li H, Cheng X, Wang X, Li L, Zhou T, et al. Preclinical pharmacokinetic/pharmacodynamic models to predict schedule-dependent interaction between erlotinib and gemcitabine. Pharm Res. 2013;30(5):1400-8.
[3] Conley SJ, Gheordunescu E, Kakarala P, Newman B, Korkaya H, Heath AN, Clouthier SG, Wicha MS. Antiangiogenic agents increase breast cancer stem cells via the generation of tumor hypoxia. Proc Natl Acad Sci U S A. 2012;109:2784-9.
[4] Jingyu L, Tianyan Z. Simultaneous determination of sunitinib and its active metabolites N-

desethylsunitinib (SU12662) in nude mice plasma by liquid chromatography tandem mass spectrometry and its application to a pharmacokinetic study. J Chin pharm Sci. 2015;24(4).

I-38: *Paul Healy* Model-based dose selection of tocilizumab for the prevention of reperfusion injury.

Paul Healy (1), Pauline P. Thémans (1), J-P. Casas (2), Oscar Della Pasqua (1)
(1) Clinical Pharmacology & Therapeutics, School of Pharmacy, University College London, (2) Institute of Health Informatics, Faculty of Population Health Sciences, University College London.

Objectives: Whereas moderate C-reactive protein (CRP) elevation in the general population is linked to long-term risk of coronary heart disease, an exponential, acute escalation of CRP following myocardial infarction (MI) has been found to be associated with increased risk of death and cardiac complications [1]. Tocilizumab (TCZ), a humanized monoclonal antibody that inhibits IL-6 receptor-binding, is currently indicated in rheumatoid arthritis and juvenile idiopathic arthritis (dosages of 4-12mg/kg). We assessed the dose rationale for preventing reperfusion injury in patients subjected to percutaneous coronary angioplasty (PCA) following an acute MI. To be efficacious in the proposed indication, tocilizumab effects on CRP levels must be clinically significant within 48h post-dose.

Methods: Pharmacokinetic (PK) and pharmacodynamic (PD) parameter data (such as clearance rate, volumes of distribution of TCZ and endogenous production rates of CRP production) from published literature were used with hierarchical modelling to assess the impact of different TCZ doses on CRP levels. An existing PK model [2] enabled the simulation of plasma TCZ concentrations, which were then used as input into a final pharmacokinetic-pharmacodynamic (PKPD) model to describe the inhibitory effects of TCZ on CRP levels. Clinical trial simulations were performed using a cohort of virtual 'at-risk subjects' assembled from the NHANES database to characterise the overall response to different TCZ doses ranging from 4-16mg/kg, proposed to treat patients post-MI in a hospital setting.

Results: Our results show that a single intravenous infusion (IV) at 4mg/kg per dose produces significant inhibition levels within 150h after administration of a single dose. Higher doses of 8mg/kg and 12mg/kg only demonstrated a prolonged, dose-dependent effect of TCZ on CRP, without a significantly faster onset of action.

Conclusion: In conclusion, modelling and simulation has allowed us to inspect the dose rationale for TCZ in a new indication. However, our analysis suggests that CRP inhibition reached within 48h may not translate into a protective anti-inflammatory response.

References:
[1] Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. J Intern Med. 2008 Oct;264(4):295-314.
[2] Frey N, Grange S, Woodworth T, Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis, J Clin Pharmacol. 2010;50 754-766.

I-39: *Michael Heathman* A Categorical Time Course PKPD Model Describing the Effect of Ixekizumab on Improvement from Baseline in Psoriasis Area and Severity Index (PASI) score in Patients with Moderate to Severe Plaque Psoriasis

Nieves Velez de Mendizabal(1), Emmanuel Chigutsa(1), Michael Heathman(1), Siak-Leng Choi(2), Laiyi Chua(2), Stuart Friedrich(1), Kimberley Jackson(3)
(1) Eli Lilly and Company, Indianapolis, IN, USA; (2) Lilly-NUS Centre for Clinical Pharmacology, Singapore; (3) Eli Lilly and Company, Windlesham UK

Objectives: The Psoriasis Area and Severity Index (PASI) score is a clinical tool for evaluating the severity and extent of psoriasis and the score ranges from 0 (no disease) to 72 (most severe disease). Ixekizumab is a monoclonal antibody that selectively binds and neutralizes interleukin 17A and has shown high levels of efficacy in the treatment of psoriasis [1]. The aim of this work is to describe and quantify the effect of ixekizumab on the PASI percent improvement from baseline scores (PASI 50/75/90/100) over time in patients with moderate to severe plaque psoriasis using a longitudinal PKPD model.

Methods: Data up to Week 32 from a Phase 2 study (N=141 patients), and data up to Week 60 from a Phase 3 study (N=1296) were included in the analysis. Phase 2: Ixekizumab was administered subcutaneously (SC) at doses from 10 to 150 mg at weeks 0, 2, 4, 8, 12, and 16. Phase 3: Ixekizumab 80mg SC was dosed every 2 or 4 weeks (Q2W or Q4W) during an induction period (up to Week 12). A starting dose of 160 mg was administered at Week 0. Responders to ixekizumab at Week 12 were randomly assigned to 80 mg Q4W, Q12W, or placebo, while nonresponders (ixekizumab and placebo) received 80mg Q4W. Responders to placebo remained on placebo or until relapse when they were switched to 80mg Q4W. Sequential PKPD model was conducted using NONMEM 7.3. Posthoc ixekizumab concentrations and area under the curve (AUC) estimates from a population PK model were used as the exposure inputs to an indirect latent variable response PKPD model.

Results: The developed model is able to simultaneously describe PASI 50/75/90/100 over time. The drug effect was best described by two different components: (i) an E_{max} model on the Type III indirect latent variable response model, with EC_{50}=1.47 µg/mL; (ii) a direct effect of AUC on the logit model for cumulative probabilities (proportional odds model) defined as E_{MAXD}×log(AUC+1) where E_{MAXD}=0.419. The placebo effect was included as a direct effect on the logit model with a sigmoidal time function, described with parameters, PL_{50}=1.67 weeks and PL_{MAX}=1.23. The PKPD model described the data well when evaluated using the treatment adaptive simulations which mimicked the complexity of the Phase 3 adaptive study design.

Conclusions: The developed latent variable indirect response PKPD model well described the time course of PASI percent improvement in patients with moderate to severe plaque psoriasis.

References:
[1] Griffiths CE, et al. UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015 Aug 8;386(9993):541-51.

I-40: *Andrea Henrich* PK/PD model extension to characterise bone marrow exhaustion in cancer patient making use of a prior paclitaxel PK model

Andrea Henrich (1,2), Markus Joerger (3), Stefanie Kraff (4), Ulrich Jaehde (4), Wilhelm Huisinga (5), Charlotte Kloft (1), Zinnia P. Parra-Guillen (1)
(1) Dept. Clinical Pharmacy & Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) and Graduate Research Training program PharMetrX, Germany, (3) Dept. of Oncology & Haematology, Cantonal Hospital, St Gallen, Switzerland, (4) Dept. Clinical Pharmacy, Institute of Pharmacy, Universitaet Bonn, Germany and (5) Institute of Mathematics, Universitaet Potsdam, Germany

Objectives: Due to complex, non-linear pharmacokinetics (PK) including high inter-individual variability and severe toxicity, especially neutropenia (pharmacodynamics (PD)) of paclitaxel (PTX), dose-individualisation and therapeutic drug monitoring are indicated. A population PK/PD model [1] was externally evaluated using data from the CEPAC-TDM trial [2]. Worsening neutropenia over repeated chemotherapy treatment cycles, we hypothesised this process could be due to bone marrow exhaustion (BME). The aim of this work was to refine our PK model and implement BME to describe neutrophil concentrations in cancer patients over several cycles.

Methods: Patients (n = 183) received PTX (doses adjusted according to a published algorithm [1]) in combination with a carbo- or cisplatin every 3 weeks for ≤ 6 cycles. PTX plasma concentrations were measured approx. 24 h after PTX administration, while neutrophil concentrations were obtained on day 1 and 15 ± 2 of each cycle. A stepwise analysis was performed: First, the prior information from the published PK model was utilised applying the frequentist approach for re-estimating the PK parameters. Second, to implement BME in a mechanistic way, an additional compartment was added to the Friberg model [3] accounting for slowly proliferating stem cells, while the proliferation compartment mimicked the rapidly dividing progenitor cells. Therefore, both cell types were replicating with different proliferation rate constants, but were influenced by the same drug effect and feedback mechanism. NONMEM 7.3, PsN 4.4 and Xpose4 4.5.3 were used.

Results: Only Km and bilirubin on Vmax of the saturable elimination of the re-estimated fixed-effects PK parameters, were outside the 90% confidence interval reported for the original PK model. However, the visual predictive check indicated a better PTX prediction than with the original PK model. The optimised PK/PD model was able to describe the observed BME pattern and showed high parameter precision (RSE < 10% for fixed- and < 20% for random-effects parameters). The proliferation rate constant of the progenitor cells was 3.67-fold higher than the one of the stem cells.

Conclusions: Using the frequentist approach previous knowledge from the former rich data were successfully combined with the sparse CEPAC-TDM study data, thus enabling an adequate description of PTX PK. A pathophysiologically plausible PK/PD model was developed to describe the hypothesised bone marrow exhaustion.

References:
[1] M. Joerger, S. Kraff, A.D.R. Huitema, et al. Evaluation of a pharmacology-driven dosing algorithm of 3-weekly paclitaxel using therapeutic drug monitoring: a pharmacokinetic-pharmacodynamic simulation study. Clin Pharmacokinet (2012) 51(9): 607–17.
[2] A. Henrich, M. Joerger, W. Huisinga, et al. External evaluation of a PK/PD model describing the time course of paclitaxel and neutropenia in patients with advanced non-small cell lung cancer. PAGE 24 (2015)

Abstr. 3460 [www.page-meeting.org/?abstract=3460].
[3] L.E. Friberg, A. Henningsson, H. Maas, et al. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J. Clin. Oncol. (2002) 20(24): 4713–21.

I-41: *Christoph Hethey* Impact of the intracellular ribosomal concentration on in vitro bacterial growth kinetics and the antibacterial effect of linezolid on S. aureus in time-kill assays

Christoph Hethey (1,2), Sebastian G. Wicha (2,3), Charlotte Kloft (2,3), Wilhelm Huisinga (2,4)
(1) Institut für Biochemie und Biologie, Universität Potsdam; (2) Graduate Research Training Program PharMetrX: Pharmacometrics & Computational Disease Modelling; (3) Institute of Pharmacy, Dept. Clinical Pharmacy & Biochemistry, Freie Universität Berlin and (4) Institut für Mathematik, Universität Potsdam

Objectives: Ribosomes are a central constituent of bacterial growth and as well of bacterial growth inhibition alike. They are targets of multiple antibiotic classes, and yet the intracellular ribosomal concentration (IRC) is commonly ignored in most pharmacodynamic modelling approaches for antibiotics. Our objective was to develop a simple bacterial growth model to analyse time-kill curve data, which explicitly describes intracellular ribosomal accumulation and dilution processes.

Methods: We used data for *S. aureus* exposed to the protein biosynthesis inhibitor linezolid. Observations on single cell level in drug-free control experiments [1] were combined with time-kill curve data, in which lag and exponential phase cultures were analysed [2]. A unified model was developed to describe the growth dynamics of both cultures during drug exposure. Following a mechanistic approach, we integrated drug effects on the cellular level and linked the perturbed cellular characteristics to population growth. Visual data exploration, parameter estimation, model diagnostics and simulations were performed in Matlab 2015a.

Results: The initial value for IRC naturally accounted for delayed growth kinetics observed in control experiments during the lag phase. Over time, IRC increased and approached a quasi steady state in the exponential phase. On the observed lag phase bacteria, the drug potency was initially decreased by approximately one order of magnitude in comparison to the exponentially growing culture. The IRC scaled linearly with the potency of linezolid and thus factored in the differences of antibacterial effects on lag and exponential phase cultures.

Conclusions: Cellular characteristics, such as IRC, deliver powerful support when modelling bacterial population growth. The lag phase, as an emergent observation on the population level, can be interpreted as the result of differences on the cellular level. A mechanistic integration of drug effects paves the way to predict drug-drug interactions when modelling bacterial growth kinetics.

References:
[1] Martin, S. E., & Iandolo, J. J. (1975). Translational Control of Protein Synthesis in Staphylococcus aureus. Journal of Bacteriology, 122(3), 1136–1143.
[2] Wicha, S. G., Kees, M. G., Kuss, J., & Kloft, C. (2014). Pharmacodynamic and response surface analysis of linezolid or vancomycin combined with meropenem against Staphylococcus aureus. Pharmaceutical Research, 32(7), 2410–2418.

I-42: *Jennifer Hibma* Population Pharmacokinetic/Pharmacodynamic Evaluation of the Effect of Inotuzumab Ozogamicin on QT Intervals in ALL and NHL Patients

Hibma, Jennifer; Boni, Joseph; Ruiz, Ana
Pfizer

Objectives: Inotuzumab ozogamicin (InO; PF-05208773) is a humanized anti-Cluster of Differentiation 22 (CD22) monoclonal antibody conjugated to calicheamicin, a potent cytotoxic antibiotic. InO is being studied for the treatment of adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). The objective of this analysis was to characterize the exposure-response relationship between heart rate corrected QT interval (QTc) and InO concentrations.

Methods: Data from clinical studies with InO monotherapy included 2743 observations from 250 patients with relapsed or refractory B-cell ALL and relapsed or refractory NHL. Serial 12-lead triplicate-ECGs were collected at screening, just prior to first dose (baseline), at predefined time points post dose and collected within 24 hours of scheduled PK collections. First the effect of InO on heart rate interval (RR interval) was evaluated prior to correcting QT. Then, the most appropriate correction factor(s) were selected (ie, Bazett's (QTcB), Fridericia's (QTcF), or a Study Specific (QTcS)) to obtain QTc values independent of the underlying heart rate. Next, a linear mixed effects model was used to describe the exposure response relationship between InO concentration and QT interval using the appropriate correction factor(s). Analyses were conducted using a population analysis approach and linear mixed effects models (NONMEM, Version 7.3.0, ICON Development Solutions, Dublin, Ireland). Full model development involved testing for covariates (both continuous and categorical) with the goal of describing the inter-individual variability (IIV) and improving predictive performance. Parameterization of covariate models was guided by examination of the plots of the IIV on slope and intercept versus covariates from the final base model.

Results: InO did not affect RR intervals. Using both the QTcF and QTcS correction factors, the QTc intervals had a positive correlation with InO concentration. The typical population slope estimate was 0.00649 (95% CI: 0.003-0.013) for the relationship between QTcF and InO serum concentration, and was 0.00695 (95% CI: 0.002-0.015) for the relationship between QTcS and InO serum concentration.

Conclusions: Based on 1000 simulations, the expected changes from baseline (QTcF and QTcS, median and upper 95% CI), at both therapeutic and supratherapeutic concentrations, were below 10 msec (QTcF 2.53 msec (4.92 msec) and 2.70 msec (5.40 msec), respectively; QTcS 3.87 msec (7.54 msec) and 4.14 msec (8.28 msec), respectively.

I-43: *Eef Hoeben* Viral Kinetic Modeling of HCV RNA Decline during Treatment with Simeprevir in Combination with Sofosbuvir

E. Hoeben (1), A. Vermeulen (1), M. Neyens (1), L. Vijgen (2) and F. De Ridder (3)
Janssen Research and Development, Clinical Pharmacology and Pharmacometrics (1), Clinical Virology (2), Statistics and Decision Sciences (3), Turnhoutseweg 30, B-2340 Beerse, Belgium

Objectives: Prediction of treatment outcome in chronic hepatitis C for patient management has become obsolete due to very high SVR rates and excellent tolerability associated with contemporary interferon free regimens[1]. Nevertheless, our objective was to evaluate whether the Neumann viral kinetic (VK) model[2], previously applied to HCV RNA data on interferon-based therapies, could be used to analyze the HCV RNA decline during treatment with 2 direct-acting antiviral agents (DAAs) and whether VK parameters could still be linked to clinical outcome. Plasma HCV RNA data obtained during 8 or 12 weeks of treatment with simeprevir (SMV) and sofosbuvir (SOF) from the COSMOS (N=167) and OPTIMIST-1 (N=310) and -2 (N=103) trials were used.

Methods: A modification of the classical Neumann-VK model[2] was used for the analysis. The model was re-parametrized to obtain the hidden instantaneous virion production (J) and required only 4 parameters (baseline viral load (V_0), inhibition of virion production (e), infected hepatocyte death rate (d) and virion clearance (C)) which could be estimated from the observed HCV RNA profiles. The model was fitted to the HCV RNA time profiles in NONMEM[3] using the SAEM algorithm. The modified VK model was evaluated using goodness-of-fit plots[4]. A logistic regression model was used to describe the relationship between the subject's virion production at the end of SMV/SOF therapy, *ie* week 8 (J_8) or week 12 (J_{12}), and SVR12. J_8 and J_{12} were derived from the individual subject's estimates of the 4 model parameters.

Results: The VK model captured the HCV RNA profiles well and the VK parameters were well estimated with considerable amount of inter-individual variability; shrinkage of the random effects was limited. For a treatment duration of 12 weeks, there was no relation between J_{12} and SVR12. For a treatment duration of 8 weeks, the probability of SVR12 decreased with increasing J_8, but this relationship was not statistically significant. The relationship was also not strong enough to allow individual predictions of SVR12.

Conclusion: On-treatment VK parameters derived from the adapted Neumann model from patients treated for 8 or 12 weeks with SMV/SOF were not able to predict SVR12. This illustrates the limitations of the Neumann model and is consistent with the observation that on-treatment HCV RNA data have no value to predict efficacy outcome in combination regimens of highly effective DAAs.

References:

[1] Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus. Hepatology, 62:932-954, 2015.
[2] Neumann, A. U. et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 282, 103–107 (1998).
[3] NONMEM Users Guides (1989–2009). Beal SL, Sheiner LB, Boeckmann AJ, and Bauer RJ (eds). Icon Development Solutions, Ellicott City, MD.
[4] Karlsson MO and Savic RM. Diagnosing model diagnostics. CPT, 82(1):17-20, 2007.

I-44: *Christian Hollensen* Estimation of random variance in NONMEM using different approaches

Christian Hollensen
Quantitative Clinical Pharmacology, AstraZeneca

Objectives: To explore the implication of estimating the variance of random effects as a random effects or fixed components in NONMEM.

Methods: A PK data set consisting of 100 subjects was simulated using a 2 compartment model with first order absorption and repeated 100 times [1]. 3 different estimation methods scenarios were explored: (1) Changing the variance estimation of IIV random effects from random to fixed components, (2) changing the variance estimation of random errors from a random to a fixed component and (3 changing the variance estimation of random errors from a random to a fixed component with data points below level of quantification using the M3 method with lower limit of quantification (LLOQ) at 4 four levels (15 %, 25 %, 35 % and 50 % LLOQ of data set). All simulations and estimations were performed in NONMEM V7.3.0 using similar initial estimates. The estimated post hoc parameters were compared to the simulated parameters to quantify the absolute relative deviation of the two estimation method in each of the 3 scenarios for every subject.

Results: NONMEM post hoc estimations were found for all data sets. In scenario (1) the mean deviation was smaller using fixed effects to estimate the variance of IIV random effects except for clearance. The difference ranged from 0.008 % for clearance to 3.4 % for central volume. In scenario (2) the mean deviation was smaller using fixed effects to estimate the variance of random errors. The difference ranged from 0.005 % for clearance to 7.3 % for the central volume. In scenario (3) the mean deviation increased with increasing proportion of LLOQ data points. The mean deviation was smaller using fixed effects to estimate the variance of the random errors.

Conclusions: NONMEM seems to have irregular behavior when estimating the variance of random effects as random or fixed components even though likelihood function should be the same. This work suggests that random effects in general should be estimated as fixed component. Further analysis on simpler and more complex models with differing initial estimates should be performed in order to further illuminate the degree of irregularity and to guide future modelling approaches in NONMEM.

References:
[1] Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2010 Jun;37(3):305-8.

I-45: *Xiao Hu* Population pharmacokinetic analysis of fampridine in Japanese patients with multiple sclerosis in a Phase 3 study

Xiao Hu (1), Lahar R. Mehta (1), Pratapa Prasad (1)
(1) Biogen, Cambridge, MA

Objectives: To characterize the pharmacokinetic (PK) profiles of fampridine in Japanese patients with multiple sclerosis in a Phase 3 study using sparse PK data.

Methods: One hundred and one subjects were randomized (Week 1) to receive either prolonged-release fampridine 10 mg tablets (n=51) or placebo (n=50) twice daily for 14 weeks. Two sparse post-dose PK samples per patients were taken during Week 9 visit. PK samples were also taken during unscheduled visit. The current data set was compared to historic data set, which were collected from mostly Caucasian subjects. Population PK was developed using NONMEM [1].

Results: The PK profiles in Japanese subjects were consistent with historic PK data, which were collected mostly from Caucasian subjects [2]. The disposition of fampridine was well described using a one-compartment linear model with a first-order absorption rate, using the same structural base model for historic data. No covariate showed significant effect on PK parameters. Visual predictive checks supported the adequacy of the model. The clearance was 41.3 L/h, the volume of distribution was 91.1 L, the absorption rate was 0.168 h^{-1}.

Conclusions: A population PK model was developed to describe the PK in Japanese patients to support further development of fampridine in this population.

References:
[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.
[2] Weir S, Gao Y, Henney HR 3rd. Population pharmacokinetics and pharmacodynamics of dalfampridine-ER in healthy volunteers and in patients with multiple sclerosis, Curr Med Res Opin. 2013 Dec;29(12):1637-45.

Study sponsored by: Biogen

I-46: *Shuhua Hu* Use of interim analysis to improve efficiency of clinical trial simulations in treatment comparison trial design studies

Shuhua Hu, Vitalii Nazarov, Kevin Feng, Michael Dunlavey, Robert H. Leary, Michael Tomashevskiy
Certara/Pharsight, Cary, NC, USA

Objectives: Clinical trial simulation (CTS) using Monte Carlo (MC) technique has been increasingly used in pharmaceutical industry to make drug development more efficient, robust and informative. However, it is time-consuming due to the large number of virtual individuals simulated. In the case where MC simulations are used to compare two treatment arms, we propose to use interim analysis (e.g., see [1, 2]) to avoid simulating unnecessary large number of subjects and hence improve the efficiency. The goal here is to demonstrate this approach through an example.

Methods: The example used to demonstrate this is based on the study conducted in [4], where MC simulation was used to confirm that the proposed dosing regimen and the approved one have equivalent clinical outcomes. This was done in [4] through comparing the steady-state time-concentration profiles between these two dosing regimens, where 100 replicates were simulated with each replicate consisting of 100 virtual individuals for each dosing regimen. Instead of visually comparing the steady-state time-concentration profiles of these two treatment arms, we borrowed the FDA standard for the bioequivalence study (e.g., see [3]), 90% confidence interval of ratios of the area under the concentration time curve (AUC) of the two dosing regimens contained in the range of 80%-125% (same rule applies to the peak plasma concentration, Cmax), to ascertain whether they are equivalent. The repeated confidence interval approach [2] was used to determine whether these two treatment arms are equivalent and when to stop the simulation. Specifically, an innovative simulation engine using Pharsight modeling language was used to simulate one subject at a time, and the repeated confidence interval approach was used to ascertain whether the simulation can be stopped.

Results: Numerical results show that after simulating 30 replicates, these two dosing regimens were found to be equivalent. This eliminates the need for simulating another 70 replicates as done in [4] to obtain the same conclusion, and hence reduces the simulation time.

Conclusions: This example demonstrates that interim analysis combined with simulation engine using Pharsight modeling language can be used to improve the efficiency of clinical trial simulations in treatment comparison studies and create statistical results for decision-making.

References:

[1] C. Jennison and B.W. Turnbull, Group sequential methods with applications to clinical trials, Chapman and Hall/CRC, Boca Raton, FL, 1999.
[2] C. Jennison and B.W. Turnbull, Interim analysis: the repeated confidence interval approach, J. R. Statist. Soc. B, 51 (1989), 305-361.
[3] S. Rani and A. Pargal, Bioequivalence: an overview of statistical concepts, Indian J. Pharmacol, 36 (2004), 209-216.
[4] Yim, etc., Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis, J Clin Pharmacol., 45 (2005), 246-256.

I-47: *Stephen Duffull* The influence of parameterisation on local identifiability

Vittal Shivva (1), Stephen Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin, New Zealand

Objectives: PK and PKPD models are often complicated due to the inclusion of mechanistic elements to improve their predictive performance. In some circumstances they may be developed from systems models using formal methods of model order reduction. In all circumstances it is important to assess the identifiability of the model to ensure that it can be used for estimation purposes. Identifiability has been extensively studied and formal methods are available for fixed effects models. Recently, local identifiability analysis has been generalized to the mixed effects model framework [1]. The aim of this work is to explore the influence of parameterization of a simple nonlinear mixed effects model on the identifiability of the fixed and random effects parameters.

Methods: Local identifiability was established by generalising the principle that |J'J|=0 (where J is the Jacobian matrix and |.| signifies the determinant) for models that are not locally identifiable due to rank deficiency [2]. However, because of numerical issues with computation of the Fisher information matrix (FIM) for nonlinear mixed effects models the criteria for (practical) local identifiability was defined as the |FIM| monotonically approaches an asymptote as the residual variance approaches zero, for identifiable models [1].

In this work we consider two parameterisations of the simple one compartment first-order input-output model:

(i) {CL, V, ka, F, var(CL), var(V), var(ka), var(F), sigma2} and

(ii) {k, V, ka, F, var(k), var(V), var(ka), var(F), sigma2}

Results: For this simple model we see that: (1) F is not identifiable in either parameterisation, (2) var(F) is identifiable in parameterisation (i) but not in parameterisation (ii), (3) parameterisation (i) is identifiable if any one of F or CL or V are fixed, (4) parameterisation (ii) is only identifiable if both F or V and var(F) or var (V) are fixed.

Discussion: Even though identifiability of the fixed effects parameters for simple models is well known we see that identifiability of the associated variance of the random effects is not always obvious. Importantly we see that local identifiability is dependent on parameterisation.

References:
[1] Shivva et al CPT:PSP 2013,2(6):1-9; e49, doi:10.1038/psp.2013.25
[2] Jacquez et al Math Biosci 1985;77:201-227

I-48: *Manuel Ibarra* Pharmacokinetic characterization of naphtalophos in lambs by modelling blood acetylcholinesterase activity, a K-PD model

Ibarra M (1), Suarez G (2), Salada S (2), Martínez I (2), Montero J (2), Vázquez M (1), Fagiolino P(1).
(1) Department of Pharmaceutical Sciences, Faculty of Chemistry, Universidad de la República. Uruguay. (2) Laboratory of Pharmacology, Faculty of Veterinary, Universidad de la República. Uruguay.

Objectives: Naphthalophos (NAF) is a widely used organophosphate for the control of sheep gastrointestinal nematode infection. In this work, a K-PD model [1] was developed to describe acetylcholinesterase activity after NAF oral administration in order to estimate absorption rate and residence time.

Methods: One hundred (100) Corriedale lambs were involved in the current experiment under regular field conditions (Uruguay). The animals were randomly allocated into five groups (n=20 each): an untreated control group and four groups treated with a single NAF oral dose of 10, 30, 50 and 70 mg/kg of Tritom NF ® (NAF 15%, Cibeles S.A.). Twenty-five animals (5 of each group) received the dose in fasting conditions. Five blood samples per animal were obtained over the 28 days post-dosing period. Samples were immediately stored and kept at -18°C until analysis. Acetylcholinesterase activity in red blood cells (AChE, µmol/mL/min) was determined using a modified Ellman assay. Population analysis was done in NONMEM 7.3 [2].

Results: A virtual two compartment model with first order absorption was used to predict NAF amount in blood after administration. Two routes were included for NAF elimination from central compartment: one involving AChE inhibition and a parallel first-order process. AChE activity versus time data was described by a turnover model with zero-order input and first-order elimination (kout). Stimulation of kout by NAF according to an indirect response model was included to describe its inhibitory effect of AChE activity. Interindividual variability was included for AChE baseline and NAF first-order absorption rate (ka). Typical estimates for AChE baseline and kout were 1.64 µmol/mL/min and 0.0129 h-1 respectively. NAF dose-proportionality on AChE inhibition was well captured by the model; estimates for maximum kout stimulation and NAF amount producing 50% of maximum effect were 20.3 and 0.709 mg/kg respectively. NAF oral absorption was independent of dose and food administration, with an estimated ka of 1.06 h-1. Simulated NAF pharmacokinetic model predicts a 14 day post-dosing period before complete washout of the drug.

Conclusions: The model described AChE typical tendency and captured interindividual variability. A pharmacokinetic profile for NAF was obtained, allowing estimation and population analysis of NAF input and disposition kinetics. This model could be further used to assess systemic NAF exposure produced after administration of the different formulations marketed in Uruguay.

References:
[1] Jacqmin P, Snoeck E, van Schaick EA, Gieschke R, Pillai P, Steimer JL, Girard P. Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. J Pharmacokinet Pharmacodyn 2007;34(1): 57-85.
[2] Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J. NONMEM User's Guides 1989-2009; Icon Development Solutions, Ellicott City, MD, USA, 2009

I-49: *Moustafa Ibrahim* The Hot Integrated Glucose-Insulin Minimal Model

Moustafa M.A. Ibrahim (1), Anna Largajolli (2), Mats O. Karlsson (1), Maria C. Kjellsson (1)
(1) Department of Pharmaceutical Bioscience, Uppsala University (2) Clinical Pharmacology Modelling and Simulation, GSK, UK.

Background and Objectives: An Integrated minimal model (IMM) has been proposed by Largajolli et al. to characterize simultaneously glucose-insulin regulation system following intravenous glucose tolerance test (IVGTT) [1]. This model was developed using the population nonlinear mixed effect modelling approach. It provides less-invasive estimates of insulin sensitivity index (SI) and glucose effectiveness index (GE) with full simulation capabilities. Since this model was developed with unlabelled IVGTT data, it cannot separate endogenous glucose production from glucose disposal, leading to a biased parametric description of glucose disposal, particularly GE reflect both mass action and control mechanism, and it overestimates fractional glucose clearance [2]. Here, we propose the hot integrated minimal model (HIMM) developed by labelled IVGTT data. We investigated as well the use of prior functionality to analyse unlabelled glucose data by IMM and obtain refined IMM parameter estimates.

Methods: Data was obtained from two previously published studies of stable isotopically labelled intravenous glucose tolerance test (IVGTT) performed in healthy subjects with one of the studies being insulin-modified [3, 4]. Frequent plasma samples were analysed to determine the concentration of total glucose, insulin, and hot glucose. The structure of the hot glucose disposition model was assumed to be identical to that of unlabelled glucose. Informative priors were obtained from one of the HIMM studies and the IMM was fitted to the other study using prior functionality in NONMEM and only total glucose observations.

Results: For the glucose sub-model, HIMM parameter estimates significantly differed from IMM parameter estimates, in particular for GE which was estimated to be twice as high in the absence of hot glucose data. VPCs from these two models were similar albeit the different parameter estimates. Parameters of insulin sub-model were accurately estimated from unlabelled data. The use of priors did not provide a solution to the biased estimates of glucose disposal.

Conclusion: The HIMM estimates GE and SI from labelled IVGTT data, without the inhibitory effects of glucose and insulin on hepatic glucose production, and so GE provides an unbiased estimate of fractional glucose clearance. Our analysis suggests that priors do not offer a suitable alternative in absence of labelled glucose data.

References:
[1] Largajolli A., Bertoldo A.,Cobelli C., and Denti P., An integrated glucose-insulin minimal model for IVGTT, PAGE 22 (2013) Abstr 2762 [www.page-meeting.org/?abstract=2762]
[2] Avogaro, A., J. D. Bristow, D. M. Bier, C. Cobelli, and G.Toffolo. Stable-label intravenous glucose tolerance test minimal model. *Diabetes* 38: 10481055, 1989.
[3] Vicini P, Caumo A, Cobelli C. The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity.*Am J Physiol.* 1997; 273:E1024-E1032.
[4] Vicini P, Zachwieja JJ, Yarasheski KE, Bier DM, Caumo A, Cobelli C. Glucose production during an IVGTT by deconvolution: validation with the tracer-to-tracee clamp technique. *Am JPhysiol.* 1999; 276:E285-E294

I-50: *Diane-Charlotte Imbs* Modeling and simulation for improving the efficacy of the combination between antiangiogenic and chemotherapy in Non Small Cell Lung Cancer

Diane-Charlotte Imbs(1), Raouf El Cheikh(1), Joseph Ciccolini(1), Severine Mollard(1), Sarah Giacometti(1), Dominique Barbolosi(1), Sebastien Benzekry(2)
(1) SMARTc Unit, Pharmacokinetics Laboratory, Inserm S_911 CRO2 Aix Marseille University and La Timone University Hospital of Marseille, (2) Modelling Control, and Computations Unit, Institut National de Recherche en Informatique et en Automatique, Bordeaux, France

Objectives: To develop a biologically-based mathematical model that is capable of describing the impact of adding bevacizumab (B) to chemotherapy (C) for non-small cell lung cancer treatment (NSCLC). The aim is to assess, through *in silico* simulations, the benefits of the additional administration of bevacizumab and to look for the best treatment modality.

Methods: In a nonclinical proof-of-concept (POC) study, immunocompromised NSCLC-bearing mice (H460-Luc+ xenograft, n=12 per group) were treated according to three different sequences associating bevacizumab and pemetrexed – cisplatin: B and C concomitantly and two sequential schedules with a lag time of 4 days between the two treatments (B before C and C before B) administered every 14 days. Tumor growth follow-up was done for each group, by bioluminescence imaging and compared with a control group (without treatment).
A pharmacokinetic/pharmacodynamic (PK/PD) model was built to describe the tumor growth observed experimentally for each of the four groups. The growth was assumed to follow a Gompertzian law and the model includes the effects of B on the quality of tumor vasculature (1). Parameters were estimated by fitting the model to the tumor growth experimental data according to a population approach (non-linear mixed effects models) using Monolix 4.3.3 Lixoft. Different time lags for the sequential administration were tested *in silico* to find the optimal time-lag for the treatment.

Results: The POC study in NSCLC confirmed the superiority of the alternative schedule (i.e., sequential administration of B given before C) in terms of survival and tumor growth compared to other sequences, with a lower tumor growth (-54.8%) and an increase in survival of 24.9% after 50 days of treatment.
The PK/PD model was able to reproduce the tumor growth data, and identify significantly higher tumor reduction in the sequential B/C group (p-value = 0.035).

Conclusion: Preclinical POC has shown evidence for superiority of sequential administration of B and C over the standard concomitant schedule. The biological-based mathematical model can be used as an *in silico* tool in order to optimize and individualize treatment regimen for the combination of bevacizumab and chemotherapy in NSCLC.

References:
[1] Benzekry S, Chapuisat G, Ciccolini J, Erlinger A, Hubert F. A new mathematical model for optimizing the combination between antiangiogenic and cytotoxic drugs in oncology. Comptes Rendus Math. janv 2012;350(1–2):23-8.

I-51: *Itziar Irurzun-Arana* Attractor analysis of Boolean models for Systems Pharmacology Networks

Itziar Irurzun-Arana (1), José David Gómez-Mantilla (1), Iñaki F. Trocóniz (1).
(1) Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 31080, Spain.

Objectives: To provide an easy-to-use and efficient methodology to perform attractor analysis on Boolean models of Systems Pharmacology networks, guiding through the required tools and steps, and showing key outcomes and their representation and impact interpretation.

Methods: Boolean network models are the simplest discrete dynamic models in which the components of a system are represented by nodes that assume two possible states, ON or OFF (1). The state of each node is determined by its regulator nodes in the network based on transition rules known as Boolean functions. For any initial condition, Boolean models eventually evolve into a limited set of stable states known as attractors (2,3). Attractors in moderate size Boolean models are often linked to cellular steady states, cell cycles or to phenotypes. However, large-scale or highly interconnected networks as the ones used in Systems Pharmacology converge into a special type of attractor known as complex attractor. Complex attractors consist on set of states in which the system irregularly oscillates (2,3), making its interpretation difficult due to the high number of stable states involved in them. An approach to overcome this problem is to generate the probability that a given node is ON inside the complex attractor.

Results: In order to minimize the effort to implement Boolean models, run simulations and analyze the results, we developed an R framework called SPIDDOR (Systems Pharmacology for effIcient Drug Development On R). One of the new features of the SPIDDOR framework is that it identifies the different steady-states of Boolean networks, known as attractors, in order to describe the long-time behavior of a system. Once an attractor is found, a dynamic perturbation analysis can be performed in order to identify which node knockouts or persistent activations lead to considerable changes in the attractors of the system, and consequently, in the activation probability of the nodes that represent the attractor.

Conclusions: With the tools explained in this methodology, the dynamics of a biological/pharmacological system can be simulated to identify its attractors and therefore understand how perturbations may alter its behavior. The resulting models can be used to analyze signaling networks associated with diseases in order to predict the pathogenesis mechanisms and design potential therapeutic targets.

References:
[1] Wynn ML, Consul N, Merajver SD, Schnell S. Logic-based models in systems biology: a predictive and parameter-free network analysis method. Integr Biol. 2012;4(11):1323.
[2] M. Hopfensitz, C. Müssel, M. Maucher HAK. Attractors in Boolean Networks - A tutorial. Comput Stat. 2013;28(1):19–36.
[3] Saadatpour A, Albert I, Albert R. Attractor analysis of asynchronous Boolean models of signal transduction networks. J Theor Biol. 2010 Oct 21;266(4):641–56.

I-52: *Swati Jaiswal* Pharmacokinetic-Pharmacodynamic modeling of miltefosine in Leishmania donovani infected Golden Syrian Hamsters

Swati Jaiswal (1,2) Thomas PC Dorlo (3,4) Mahendra Shukla (1,2) Abhisheak Sharma (1,2,5) Brajendra Tiwari (6) Neena Goyal (6) and Jawahar Lal (1,2)

(1) Pharmacokinetics & Metabolism Division, CSIR-Central Drug Research Institute, Lucknow, India (2)Academy of Scientific and Innovative Research, New Delhi, India (3) Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands (4) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (5)Department of Pharmaceutics and Drug Delivery, The University of Mississippi, Mississippi, USA (6)Biochemistry Division, CSIR-Central Drug Research Institute, Lucknow, India

Objectives: The knowledge about the exposure-effect relationship of miltefosine (MF) is limited, which is imperative for understanding the risk factors associated with its treatment failure [1,2]. Preclinical PK-PD evaluation of MF could be a decisive approach too and can be very useful if successfully translated to clinical outcomes. Therefore, a PK-PD study was planned in *L. donovani* infected hamster model.

Methods: Multiple dose oral (10, 20 and 30 mg/kg dose daily for 5 days at 24 hr interval) PD study of MF was carried out in *L. donovani* infected Golden Syrian hamsters. During PD study 1 pre-treatment and 4 post-treatment spleen biopsies were carried out on day 7, 14, 21 and 28 and % infection [(number of amastigotes/number of macrophage) *100] was recorded as PD parameter. Twenty infected hamster received no treatment and were used for modeling base line and natural disease progression. Multiple dose oral PK studies were carried out in healthy hamsters at similar doses (n=10 hamsters, per dose group). Blood samples were withdrawn up to 28 days post treatment and harvested plasma samples were analysed using LC-MS/MS [3]. The PK model was developed first and thereafter the PD model, using a sequential fit with fixed population PK parameters. Analysis was conducted using FOCE I in NONMEM 7.3.0. Xpose and PsN were used for graphical evaluation and model diagnostics.

Results: A one compartment model provided the best fit to the PK data. The estimated typical value for absorption rate constant (k_a), oral clearance (CL/F) and oral volume of distribution (V/F) were 0.391 h^{-1}(0.097), 0.012 L/h/kg (0.044) and 1.15 L/kg (0.037). BSV in CL/F and k_a were modelled with an exponential error. BSV in k_a and CL were estimated to be 32% and 11%, respectively. RUV was characterized by a proportional error model and found to be 30%. The final PK-PD model was composed of a base line model with proportional disease progression and an effect compartment-inhibitory sigmoidal E_{max} model with symptomatic drug effect. This model best described the data with adequate VPC and basic goodness of fit plots. The estimated value for baseline in terms of % infection is 15 and the disease progression rate (α) is 0.011 h^{-1}. The estimated plasma EC_{50} for MF is 0.32 mg/L and maximum response (E_{max}) is 0.95 % (93 % reduction in baseline % infection value).

Conclusions: The final PK-PD model described the data well and can be used for studying drug effects in hamster from MF mono-therapy.

References:

[1] Sundar S, Singh A, Rai M, Prajapati VK, Singh AK, Ostyn B, Boelaert M, Dujardin JC, Chakravarty J. Efficacy of miltefosine in the treatment of visceral leishmaniasis in India after a decade of use. Clin Infect Dis (2012) 55(4):543-50.

[2] Rijal S, Ostyn B, Uranw S, Rai K, Bhattarai NR, Dorlo TP, Beijnen JH, Vanaerschot M, Decuypere S, Dhakal

SS, Das ML, Karki P, Singh R, Boelaert M, Dujardin JC. Increasing failure of miltefosine in the treatment of Kala-azar in Nepal. and the potential role of parasite drug resistance, reinfection, or noncompliance. Clin Infect Dis (2013) 56(11):1530-8
[3] Jaiswal S, Sharma A, Shukla M, Lal J. LC-coupled ESI MS for quantification of miltefosine in hamster and human plasma. Bioanalysis (2016): *Accepted manuscript*.

I-53: *Masoud Jamei* Time variation in the fractional contribution of an enzyme to elimination of a victim drug can explain differences in DDI susceptibility following single and multiple dosing

Oliver Hatley (1), Rachel H. Rose (1), Masoud Jamei (1)
(1) Simcyp Ltd (a Certara Company), Sheffield, UK

Objectives: The fractional contribution of an enzyme to systemic elimination (fm) is an important determinant of the drug-drug interaction (DDI) potential of a victim drug. In static DDI predictions, fm is assumed to be constant. However, this assumption is not valid for victim drugs that show for example metabolism saturation or time-dependent inhibition (autoinhibition) of one or more of their own metabolic pathways. Time variation in the fm of CYP2D6 and CYP3A4 was investigated for paroxetine, which is both a substrate and a potent mechanism-based inhibitor (MBI) of CYP2D6.

Methods: Multiple daily dosing of 30 mg paroxetine for 21 days was simulated in the Simcyp Simulator V15.1 for CYP2D6 extensive metabolisers (EMs) and poor metabolisers (PMs) using the built-in Sim-Healthy Volunteer population library and SV-Paroxetine compound file. The paroxetine model includes MBI for both CYP2D6 and CYP3A4. DDI with ketoconazole (400mg QD for 8 days) was simulated for paroxetine on day 1 and day 21. Dynamic variation in fm for CYP2D6 and CYP3A4 was considered for paroxetine, assuming a well-stirred liver model and accounting for the minor contribution of renal elimination.

Results: For CYP2D6 EMs, the fm CYP2D6 was 0.97-0.98 for the first dose paroxetine, and decreased to 0.54-0.71 on day 21 as a result of MBI. The reported range of fm values for EMs reflect concentration sensitivity of MBI, as well as a progressive change in fm over time. The fm CYP3A4 was 0.016-0.021 for the first dose and increased to 0.22-0.35 on day 21, which corresponded to an increase in the predicted AUC ratio in the presence of ketoconazole from 1.13 (day 1) to 1.97 (day 21). For CYP2D6 PMs, the fm CYP3A4 was 0.77 (day 1) and 0.75 (day 21) and AUC ratio with ketoconazole was 1.21 (day 1) to 1.68 (day 21).

Conclusions: For paroxetine, autoinhibition of CYP2D6 in EMs results in a decrease in fm CYP2D6 and corresponding increase in CYP3A4 fm following multiple dosing. This observation explains an increased susceptibility to DDI with the CYP3A4 inhibitor ketoconazole following multiple dosing. The absence of CYP2D6 in PMs results in little change in CYP3A4 fm following multiple dosing and a smaller increase in ketoconazole DDI. Dynamic models that incorporate the time variation in fm can predict and explain differences in DDI liability following single and multiple dosing of a victim with autoinhibition, autoinduction or metabolism saturation.

I-54: *Félix Jaminion* Use of a drug-drug interaction study with itraconazole to quantify the effects of an NME on QT interval duration

Félix Jaminion (1), Darren Bentley (1), Michael Derks (2), Cheikh Diack (1)
(1) Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, F.Hoffmann-La Roche Ltd, Switzerland (2) Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Welwyn, Roche Products, UK

Objectives: Assess the QT interval prolonging effect at supra-therapeutic exposure of a new molecular entity (NME) using a DDI study.

Methods: A clinical DDI study was conducted to evaluate the pharmacokinetics and QT prolonging effect of the NME (mainly metabolized by CYP3A4) with and without concomitant administration of the potent CYP3A inhibitor itraconazole. The study was a fixed sequence crossover. Subjects received dose D1 (n = 4) or D2 (n = 8) of the NME b.i.d. for 10 days, 200 mg itraconazole b.i.d. for 5 days, and the NME b.i.d + 200 mg itraconazole qd for 10 days. ECGs were collected at baseline and serially paired with PK samples.

A nonlinear mixed effects modeling approach in NONMEM (version 7.2 Icon Development Solutions, Ellicott City, MD) were used for the parameters estimation and R Studio (v 0.98) and SAS (v 9.4) was used for graphical analyses of the results.

All data from the 3 treatment periods were used simultaneously to develop an exposure response model relating the different drug concentration to QT. The non-linear mixed effects modeling approach used here appropriately differentiated the drug-induced QT prolongation from other factors altering QT Interval duration. More specifically, the model uses an individualized correction of heart rate effect and incorporates oscillatory functions to describe the circadian rhythms observed in QT profiles. The potential impact of meal times which were not time-matched between baseline and post-dose was accounted by quantitating their effects on the parameters describing the diurnal variation of QT. Simulations were performed to check that the model adequately describe the data. The risk of QT prolongation for high concentrations of the NME was assessed using a PK model assuming 50% decrease of the clearance at supra-therapeutic doses.

Results: The model suggested a weak increasing effect on QT interval of the NME while Itraconazole had a slight decreasing effect. It was shown using VPC and PPC that the model describes adequately the data and that it is usable for prediction. It was shown by simulations that the upper bound of the 95% confidence interval of the mean double delta corrected QT interval would cross the 10 ms threshold only when the clearance of the NME is decrease of 50% at dose 10 fold higher than the maximum dose used in clinic.

Conclusions: A model that adequately evaluates the drug effects of the NME on cardiac repolarization was developed. It was shown that the magnitude of the NME effect on QT prolongation is unlikely to be of clinical concern even at high exposures.

References:
[1] ICH E14 Guidance. The clinical evaluation of QT/QTc interval prolongation andproarrhythmic potential for non-antiarrhythmic drugs. European Medicines Agency, November 2005
[2] Vladimir Piotrovsky. Pharmacokinetic-Pharamcodynamic Modeling in the Data Analysisand Interpretation of Drug-induced QT/QTc Prolongation., October 2005

I-55: *Carl Johansson* Omeprazole dose recommendation in pediatric patients aged 1-11 months with erosive esophagitis

Carl-Christer Johansson, Mohammad Niazi, Tommy Andersson, Ulrika Wählby-Hamrén
Quantitative Clinical Pharmacology, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Gothenburg, Sweden

Objectives: Omeprazole (PRILOSEC) 20mg once daily is approved in the US for adults with gastroesophageal reflux disease and erosive esophagitis. The label includes children >1 year of age, with a body weight adjusted dosing algorithm. A PRILOSEC sachet formulation was developed for infants and the present analysis aimed to support the dose recommendation of omeprazole in children aged 1-11 months with erosive esophagitis.

Methods: Due to the very limited PK data available (n=4) in the target population, 1-11 months, an integrative approach was taken to utilize PK and PD data from: adults, older children and for omeprazole[1,2] and esomeprazole[3,4]. Exposure-response (AUC-acid secretion) across these populations and products were assessed for justification of bridging on PK alone. A population PK model was developed based on available omeprazole pediatric data and allometric scaling of CL/F and V/F was assumed *a priori*. The age dependent maturation of CL was assessed on iv omeprazole pediatric data. Simulations with the final model were used to explore dosing options in children 1-11 months, aiming for a similar exposure (AUC) to the adult 20mg once daily omeprazole dose.

Results: The exposure-response relationship was shown to be similar in adults and children for both omeprazole and esomeprazole, thus supporting bridging of doses from adults based on PK alone. Simulations were performed based on the developed population PK model; a one compartment model with first order absorption and lag-time. The simulation model further included the maturation function on CL and a relative increase in oral bioavailability in children below 1 year that has previously been reported[5]. Simulated exposures (AUC) were over all in good agreement with the exposure derived by non-compartmental analysis. The selected doses, in children <1 year, matching the exposure in adults receiving 20 mg of omeprazole were: 2.5mg (3<5kg), 5mg (5<10 kg) and 10mg (≥ 10kg).

Conclusions: The suggested omeprazole doses (2.5, 5 and 10 mg) in children 1-11 months with erosive esophagitis are likely to demonstrate efficacy and minimize the risk that the exposure will reach levels leading to safety concerns. The PRILOSEC label was recently updated to include the presented dose recommendation for children below 1 year of age.

References:

[1] Faure C, Michaud L, Shaghaghi EK, Popon M, Turck D, Navarro J, Jacgz-Aigrain E. Intravenous omeprazole in children: pharmacokinetics and effects on 24-hour intragastric pH, J Pediatr Gastroenterol Nutr, 33:144-148, 2001. [2] Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole -- a gastric proton pump inhibitor – on pentagastrin simulated acid secretion in man. Gut, 1983 Apr:24(4):270-276 [3] Andersson T, Röhss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and Pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther, 15:1563-1569, 2001. [4] Junghard O, Hassan-Alin M, Hasselgren G. The effect of the area under the plasma concentration vs time curve and the maximum plasma concentration of esomeprazole on intragastric pH. Eur J Clin Pharmacol, 2002 Oct;58(7):453-458. [5] Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kaufman RE.

Developmental pharmacology-Drug disposition, action, and therapy in infants and children, New England Journal of Medicine, 2003: 349 (12): 1157-1167

I-56: *Lee Jong Bong* Predicted versus experimental permeability data for incorporation into GastroPlus™ for modelling and simulations

Jong Bong Lee(1), Atheer Zgair(1), Tae Hwan Kim(2), Hwi-yeol Yun(3), Peter Fischer(1), Pavel Gershkovich(1)
(1)School of Pharmacy, University of Nottingham, UK; (2)School of Pharmacy, Sungkyunkwan University, South Korea; (3)College of Pharmacy, Chungnam National University, South Korea

Objectives: Firstly, to obtain experimental permeability data for a list of compounds using simple and accessible Caco-2 cell permeability assay and compare with permeability predicted by GastroPlus™. Secondly, to assess the effect of difference between the two permeability data in simulation of pharmacokinetic profiles.

Methods:
1) Caco-2 cell permeability assay was performed using Caco-2 cell monolayer maintained for 21 days. Monolayer integrity was monitored by measurement of transepithelial electric resistance (TEER) before and after the permeability assay. 17 compounds with structural diversity (antipyrine, atenolol, cetirizine, cimetidine, desipramine, dexamethasone, furosemide, hydrochlorothiazide, ketoprofen, metoprolol, naproxen, piroxicam, propranolol, ranitidine, sildenafil, terbutaline and verapamil) were tested and apparent permeability coefficient (Papp) values were obtained. Papp values of 14 compounds were used to develop a user-defined permeability model in GastroPlus™. This model was applied to all compounds to obtain human effective permeability (Peff) from in vitro experimental data.
2) GastroPlus™ and its built-in ADMET Predictor module were used for in silico prediction of Peff values based on chemical structures of the compounds.

Results: User-defined permeability model was developed in GastroPlus™ by correlating the experimental Papp values of the 14 compounds with built-in Peff values in GastroPlus™ and a log-linear model was obtained (R^2=0.8799). The Peff values predicted from this model and Peff values from previously reported literature had a correlation of R^2=0.7375. Peff values predicted in silico by GastroPlus™ showed a correlation of R^2=0.6917 with the literature values. Peff values obtained from experimental model and Peff values obtained from in silico prediction resulted in R^2=0.6990, indicating reasonable prediction power of the software. The influence that the difference between two dataset has on outcomes of simulated pharmacokinetic profiles were assessed for dexamethasone, sildenafil and cetirizine.

Conclusions: Although GastroPlus™ was able to predict permeability of compounds with reasonable accuracy, experimentally obtained permeability data were more accurate when used in simulation of reliable pharmacokinetic profiles. In silico permeability predictions could be utilised to facilitate decision making processes but permeability remains as a value that experimentation is desired whenever possible.

I-57: *Daniel Jonker* Personalized dosing of a novel recombinant human FSH, follitropin delta, based on individual patient characteristics

Daniël Jonker (1), Lars Erichsen (2), Bjarke Mirner Klein (1) and Joan-Carles Arce (1)
(1) Ferring Pharmaceuticals A/S, Copenhagen, Denmark (2) Currently Novo Nordisk A/S, Søborg, Denmark

Introduction: Follitropin delta is a novel recombinant follicle-stimulating hormone (FSH) preparation produced by a human cell line. It has been developed for controlled ovarian stimulation in women undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). Setting the starting dose of FSH is challenged by the fact that the ovarian response varies greatly across patients given the same starting dose of FSH, and that a too high response increases the risk of ovarian hyperstimulation syndrome, which is a potentially life-threatening condition.

Objective: To establish an individualized dosing regimen for follitropin delta resulting in a more appropriate ovarian response.

Methods: The relationship between the dose of follitropin delta and the number of oocytes retrieved was studied in 222 IVF/ICSI patients randomized to daily doses of 5.2, 6.9, 8.6, 10.3 or 12.1 µg follitropin delta [1]. Randomization was stratified by serum anti-Müllerian hormone (AMH) level at screening. The number of oocytes retrieved (OR) was used as a marker for ovarian response and the dose-response relationship was described using a negative binomial model [2] implemented in NONMEM. A stepwise covariate selection procedure was applied to identify predictive factors for OR, such as the AMH level.

Results: A sigmoid Emax dose-response relation was found to describe the data adequately with weight-adjusted dose (µg/kg) being a better predictor than unadjusted dose (µg). Among five evaluated covariates, baseline AMH level explained most of the variability in OR and was the only covariate retained. The model was used to estimate, for a range of AMH levels, the dose of follitropin delta required to achieve an appropriate ovarian response. This resulted in the following proposal: a fixed daily dose decreasing from 0.19 to 0.10 µg/kg body weight by increasing AMH (maximum daily dose 12 µg) in patients with AMH ≥15 pmol/L and a fixed daily dose of 12 µg in patients with AMH < 15 pmol/L. The proposed dosing regimen was subsequently evaluated in a confirmatory Phase 3 study and resulted in the expected reduction of the number of patients with extreme ovarian response.

Conclusions: Follitropin delta is the first human recombinant FSH developed to offer women precise dosing according to their AMH levels and body weight. This dosing regimen is a new paradigm in fertility management and was established using dose-response modelling.

References:
[1] Arce J-C, Nyboe Andersen A, Fernández-Sánchez M, et al. Ovarian response to recombinant human follicle-stimulating hormone: a randomized, antimüllerian hormone-stratified, dose-response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2014, 102:1633-1640.
[2] Troconiz IF, Plan EL, Miller R and Karlsson M. Modelling overdispersion and markovian features in count data. J. Pharmacokinet Pharmacodyn 2009, 36:461-477.

I-58: *Marija Jovanovic* Population pharmacokinetic model of topiramate and its major metabolite in adult epileptic patients

M. Jovanovic (1), D. Sokic (2) I. Grabnar (3), T.Vovk (3), R. Roskar (3), D. Milosheska (3), M. Prostran (4), B. Golubovic (1), K. Vucicevic (1), B. Miljkovic (1)

(1) Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy, Serbia; (2) Clinic of Neurology, Clinical Centre of Serbia, Belgrade; (3) Department of Biopharmaceutics and Pharmacokinetics, University of Ljubljana - Faculty of Pharmacy, Slovenia; (4) Departmant of Pharmacology, Clinical Pharmacology and Toxicology, University of Belgrade - School of Medicine, Serbia.

Objectives: The aim of the study was to characterize metabolic profile of topiramate (TPM) and to assess influence of enzyme induction by carbamazepine (CBZ) on first-order rate constant of metabolite (2,3-O-des-isopropylidene TPM) formation.

Methods: Data were collected from 68 adult epileptic patients on mono- or co-therapy of TPM and other antiepileptic drugs. Daily doses of TPM were in range from 50-1200 mg and dosage regimens were once, twice or three times a day. Steady-state TPM and its metabolite concentrations were determined in blood samples (1-2 per patient) by liquid chromatography tandem mass spectrometry assay. The population pharmacokinetic (PK) analysis was performed using NONMEM® software (version 7.3) and Perl speaks NONMEM® (version 4.4.0). Parameters estimation was performed by FOCE with interaction. The influence of CBZ daily dose on first-order rate constant of metabolite formation was evaluated.

Results: Mean first-order rate constant of metabolite formation was estimated at 0.00444 h^{-1}, while first-order rate constant of metabolite elimination was 0.0106 h^{-1}. The interindividual variability was evaluated by an exponential model while residual variability was best described by proportional for parent and additive model for metabolite. Average daily dose of CBZ were 1010.5 ± 409.5 mg (range of 300-1600 mg). Daily dose of CBZ significantly ($p < 0.05$) increased parameter of elimination and interindividual variability was reduced. Among tested relations, influence of this covariate was best described by exponential model. Volume of distribution was fixed at 0.6 l/kg while first-order elimination rate constant was fixed at 0.038 h^{-1}. Acceptable model performances were confirmed by adequate diagnostic plots and internal validation.

Conclusions: The final population PK model describes and quantifies influence of CBZ daily dose on first-order rate constant of metabolite formation. The results confirm that CBZ is inducer of TPM metabolism and importance of dosage regimen adjustment in routine patient care of patient co-treated with this drug.

References:

[1] Britzi M, Perucca E, Soback S, Levy RH, Fattore C, Crema F, Gatti G, Doose DR, Maryanoff BE, Bialer M. Pharmacokinetic and metabolic investigation of topiramate disposition in healthy subjects in the absence and in the presence of enzyme induction by carbamazepine. Epilepsia. 2005;46(3):378-84.

I-59: *Matts Kågedal* Selection of exposure metrics AUC, Cmax or Cmin in exposure response analyses – a simulation study.

Matts Kågedal, Qi Liu, Jin Yan Jin
Genentech Inc

Objectives: The relation between drug exposure and response (ER) is often described based on summary metrics of exposure such as AUC, Cmax or Cmin. This analysis approach ignores time, but makes the analysis more efficient compared to longitudinal PK-PD analyses, and is commonly used in drug development and regulatory reviews. The aims of this simulation study were to understand the consequences of ignoring time in the simplified ER analysis and to understand in what situations AUC, Cmax or Cmin correlates better with response.

Methods: Longitudinal PK and PD data were simulated for three different doses based on a one compartment first order absorption PK model with 50% variability on PK parameters (CL, V and Ka) and an indirect response PD model [1] with drug effect either on the rate constants Kout or Kin. Three underlying models for the relation between drug concentrations and the effect on rate constants were tested: linear, E-max, and an E-max model with a high sigmoidicity factor (on/off like effect). AUC, Cmax and Cmin were derived and correlated with response at end of treatment

Results: The exposure metric that correlated best with response was dependent on the underlying relationship and also varied between doses for the same assumed relationship. AUC was the best metric (highest correlation with response) in the linear range. Cmin correlated best in the exposure range approaching saturation. Cmax correlated best when exposures were mostly below the EC50 for the on/off like effect. The correlation across doses covering a wide response range was highest for AUC in all cases. The ER relationships derived based on each dose group separately were in agreement only when the underlying relation was linear and AUC was used as exposure metric. In all other cases there was a discrepancy between the ER relations derived based on each dose separately, in spite of the overlapping individual exposure between doses. I.e. at the same exposure (e.g. high Cmin from low dose group and low Cmin from high dose group), the expected response differed between doses.

Conclusions: This simulation study suggests that AUC is the best metric overall for ER analyses, but the best exposure metric varies with dose and the underlying PK-PD relation. The ER relationship derived based on one dose group may not be predictive of the response of another dose. This complication may need special attention when ER assessment and dose justification is based on a single dose group.

References:
[1] Jusko WJ , Ko HC. Physiologic indirect response models characterize diverse types of pharmacodynamic effects. Clinical Pharmacology and Therapeutics [1994, 56(4):406-419]

I-60: *Tatiana Karelina* Clinical trial simulation and hypothesis testing using amyloid pathology longitudinal translational model

Tatiana Karelina (1), Oleg Demin (1), Sridhar Duvvuri (2), Tim Nicholas (2)
Institute for System Biology, Moscow, Russia, (2) Pfizer Worldwide Research and Development, Groton, CT, USA

Objectives: Amyloid (Ab) is one of the main targets in Alzheimer's disease (AD) therapy. The goal of this work was to model quantitatively longitudinal biomarker dynamics and to check whether different trial scenarios can help to distinguish between Ab toxicity hypotheses.

Methods: The proposed translational model of Ab pathology describes Ab production, clearance and distribution in brain, CSF, plasma and other tissues, as well as aggregation in brain. Multiple mouse and human data were used for model calibration, including on longitudinal data for healthy and AD subjects (brain, plasma and CSF Ab concentrations). It was externally verified using PET data for both populations and allows for translation between mouse, human and monkey. Model uncertainty was analyzed using hessian. Three simple assumptions of relationship between Ab and Adas-cog score have been formulated: (i) proportional or (ii) threshold Ab influence on Adas-cog score and (iii) Ab functional obligatoriness for neurons [1]. Their combinations gave 5 hypotheses which were implemented as explicit algebraic functions, describing the disease progression corresponding to the observed longitudinal sporadic AD data. Model was developed and analyzed using DBSolve Optimum software and R.

Results: Different therapeutic regimens were simulated: inhibition of Ab production by 20 and 50 % and activation of insoluble Ab destruction to 150% for two ages of therapy start: 70 (early) and 75 (late) years. Model predictions for different hypotheses revealed that for early therapy start no significant difference with placebo group would be seen for at least two years for all hypotheses. For later therapy start hypotheses of Ab obligatoriness predict cognitive decline at the beginning (for production inhibition) which is compensated only after two years by depletion of toxic forms. Destruction activation is less dangerous in this respect, but it requires not less than a year to observe at least 4 points of Adas-cog score diff vs placebo. Under the hypothesis of proportional toxicity and Ab obligatoriness model predictions approximately correspond to the published results of avagacestat [2] and bapineusumab [3] trials.

Conclusions: Mechanistic model allows framework for analysis of clinical trials, hypotheses formulation and optimal therapeutic design.

References:
[1] J Neurosci. 2008; 28(53):14537.
[2] Arch Neurol. 2012; 69(11): 1430.
[3] Lancet Neurol. 2010; 9(4):363.

I-61: *Anhye Kim* Population Pharmacokinetic/Pharmacoynamic Models to evaluate the positive and delayed effect of escitalopram on QT prolongation

Anhye Kim (1), Jaeseong Oh (1), Kyungho Jang (2), Su-jin Rhee (1), Kyung-Sang Yu (1), Howard lee (1)(3), In-Jin Jang (1), Jae-Yong Chung (4)

(1) Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea (2) Department of Clinical Pharmacology and Therapeutics, CHA University School of Medicine and CHA Bundang Medical Center, Seongnam, Korea (3) Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea (4) Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Korea

Objectives: Escitalopram had potential to prolong QT interval in dose-dependent manner and to show delayed QT interval prolongation [1]. To evaluate the QT interval induced by escitalopram, it is important to explain exposure-effect relationship based on a PK-PD modeling. This study aims to develop a PK/PD model of QT prolongation induced by escitalopram based on the data from the thorough QT (TQT) study and to evaluate effects of the escitalopram, placebo and sex on QT prolongation

Methods: PK and QTc data were obtained from previous TQT study in healthy volunteers (male/female) as follows: placebo 23/13 and escitalopram 21/12 [1]. The QT interval was individually adjusted (QTcI) for the heart rate for each subjects as follows: $QTcI = QT/RR^a$ (RR, the RR interval; a, an individually derived power term in the QT–RR regression). PK model of escitalopram was built using nonlinear mixed-effect model as implemented in NONMEM V7.3.0. For baseline correction, circadian effect (CIRC) on the baseline QTcI using cosine functions with up to two periods (12 and 6 hours) was explored based on the data from the placebo treatment. To explain delayed effect between PK and PD, the effect compartment model was employed. The PK-PD model included the drug and placebo effect, circadian rhythm and sex effect on QT prolongation.

Results: A one-compartment model with first-order absorption and lag time, first-order elimination and exponential error model was chosen as the final PK model for escitalopram. Circadian rhythm of baseline QTcI interval was well described. In the final PK-QTc model, QTcI interval was derived by the following equations; QTcI = (baseline of QTcI + Placebo effect + Sex) * (1 + CIRC) + slope of concentration-QTcI * concentration in effect compartment. According to the final PK-PD model, the maximal QTcI prolongation was estimated as 4.2 msec (slope (0.18 msec/ng/ml) multiplied by Cmax (23.1 ng/ml, [1])). The effect compartment equilibrium rate constant was 0.79 (1/h), and it explained a time delay between Cmax and maximal QTcI prolongation. The sex effect on QTcI prolongation was observed (+25.8 msec in female).

Conclusion: The present analysis was carried out as a follow-up study using observed data from the previous TQT study. The developed PK-PD model well described the time course of the QT interval and evaluated the effect of escitalopram on QTcI prolongation and hysteresis of escitalopram-induced QTc prolongation.

References:

[1] Kim, Anhye; Lim, Kyoung Soo; Lee, Howard; Chung, Hyewon; Yoon, Seo Hyun; Yu, Kyung-Sang; Cho, Joo-Youn; Jang, In-Jin; Chung, Jae-Yong; A thorough QT study to evaluate the QTc prolongation potential of two neuropsychiatric drugs, quetiapine and escitalopram, in healthy volunteers, International Clinical Psychopharmacology, doi: 10.1097/YIC.0000000000000124

I-62: *Anke Kip* Population pharmacokinetics of plasma and intracellular miltefosine concentrations in cutaneous leishmaniasis patients

A.E. Kip (1,2), M.A. Gomez (3), M.M. Castro (3), A. Cossio (3), J.H.M. Schellens (2,4), J.H. Beijnen (1,2,4), N.G. Saravia (3), T.P.C. Dorlo (2,5)

(1) Dept. of Pharmacy & Pharmacology, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands, (2) Div. of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, the Netherlands, (3) Centro Internacional de Entrenamiento e Investigaciones Medicas (CIDEIM), Cali, Colombia, (4) Dept. of Clinical Pharmacology, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands, (5) Dept. Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Miltefosine is the most important oral drug against cutaneous leishmaniasis (CL). Though *Leishmania* parasites reside within macrophages, the intracellular PK of miltefosine has not been studied previously. Our aim was to develop a population PK model describing both plasma and intracellular miltefosine PK in CL patients. This model will contribute to the understanding of the relation between drug exposure and treatment outcome and provides bases for alternative dosing regimens.

Methods: Fifty-one Colombian CL patients (29 children 2-12y, 22 adults ≥18y), receiving a 28-day 2.5 mg/kg/day miltefosine treatment, were included in the model. 338 plasma and 194 peripheral blood mononuclear cell (PBMC) samples were collected and analyzed with LC-MS/MS [1,2]. A population PK model was developed with NONMEM (v7.3), with both plasma and PBMC data. Weight, age, gender, fat-free mass (FFM), ethnicity and treatment center were evaluated as covariates. Precision and predictive performance of the model were assessed by bootstrap and visual predictive checks. A previously developed allometric dosing algorithm [3] was evaluated for its effect on drug exposure by simulating PK curves (1,000 simulations/individual) and predicting $AUC_{0-\infty}$. Values are reported as mean±SD.

Results: Miltefosine accumulates to a higher end-of-treatment steady-state concentration in PBMCs (75.0±65.6 µg/mL) than in plasma (26.1±6.8 µg/mL). A three-compartment model with intracellular miltefosine accumulation within the central compartment was most adequate. Distribution of miltefosine into PBMCs was best described with an intracellular to plasma ratio (2.17, RSE 29%) plus an intracellular distribution rate constant (1.15 day^{-1}, RSE 14%). FFM was a significant covariate on clearance and V_d. Addition of a maturation factor in the FFM calculation [4] significantly improved the model (ΔOFV -7.46). With linear dosing, children only reach 82% of adult $AUC_{0-\infty}$ in plasma (813±159 v. 986±184 µg·day/mL) and PBMCs (1831±652 v. 2225±785 µg·day/mL). Simulating allometric dosing, the $AUC_{0-\infty}$ in children increased to 964±169 µg·day/mL in plasma and 2173±751 µg·day/mL in PBMCs.

Conclusions: The PK of miltefosine in CL patients conforms to a three-compartment model with intracellular accumulation of the drug. Simulation of an allometric dosing shows an increase in drug exposure for pediatric CL patients, suggesting a possible improvement in miltefosine treatment outcome in children.

References:

[1] Dorlo TP, Hillebrand MJ, Rosing H, Eggelte TA, de Vries PJ, Beijnen JH. Development and validation of a quantitative assay for the measurement of miltefosine in human plasma by liquid chromatography-tandem mass spectrometry. J Chrom B (2008) 865(1-2): 55–62.

[2] Kip AE, Rosing H, Hillebrand MJ, Castro MM, Gomez MA, Schellens JH, Beijnen JH, Dorlo TP.

Quantification of miltefosine in peripheral blood mononuclear cells by high-performance liquid chromatography-tandem mass spectrometry. J Chrom B (2015) 998: 57-62
[3] Dorlo TP, Huitema AD, Beijnen JH, de Vries PJ. Optimal dosing of miltefosine in children and adults with visceral leishmaniasis. Antimicrob Agents Chemother (2012) 56(7): 3864-72.
[4] Al-Sallami HS, Goulding A, Grant A, Taylor R, Holford N, Duffull SB. Prediction of Fat-Free Mass in Children. Clin Pharmacokinet (2015) 54(11):1169-78.

Registration number in Clinicaltrials.gov: NCT01462500 Funding: COLCIENCIAS (250-2010); COLCIENCIAS (0040-2012) and Fogarty International Center of the National Institutes of Health under Training Award number D43TW006589.

I-63: *Lena Klopp-Schulze* Tamoxifen and endoxifen pharmacokinetics: Exploration of differences in model performance using simulations

Lena Klopp-Schulze (1), Markus Joerger (2), Sebastian G. Wicha (1), Zinnia P. Parra-Guillen (1), Charlotte Kloft (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Medical Oncology and Clinical Pharmacology, Dept. of Internal Medicine, Cantonal Hospital St. Gallen, Switzerland

Objectives: Two population pharmacokinetic (PK) models of tamoxifen (TAM) and its principle metabolite endoxifen (ENDX), Model 1, M1, [1] and 2, M2, [2] were built from data at steady-state (st-st); both implemented the impact of CYP2D6 and CYP3A4/5 activity but using different structural models. A previous investigation displayed considerable differences in predicted TAM (-40%) and ENDX (-20%) trough concentrations at st-st ($C_{ss,min}$) by M2 compared to M1 [3]. Good model predictions are crucial for model reuse as prior knowledge. The aim of this work was to explore potential reasons for the unexpected differences and their impact.

Methods: Three hypotheses were tested: (1) differences in bioavailability (F), (2) differences in medication adherence and (3) the assumption of st-st in M2. Simulations were performed with a multiple dosing regimen (20 mg/day p.o.) and considering similar CYP2D6 phenotype distributions in both models.

For the hypotheses (1) and (2) several populations of factor tiers (each n=1000) were simulated using M1 in Berkeley Madonna (v. 8.3.18) to reproduce predictions of M2. Daily drug intake was simulated as a binary outcome with a constant probability of non-adherence.

For hypothesis (3), concentration-time profiles (each n = 100) were simulated with M2 and then parameters re-estimated assuming st-st at different days (5, 10, reference: 20) in NONMEM (v. 7.3). Predicted parameters and resulting C_{ss} of TAM and ENDX were compared between the original and re-estimated parameter sets.

Results: Decreases in F or adherence (both 40%) in M1 were only able to reproduce predictions of $C_{ss,TAM}$ in M2, but $C_{ss,ENDX}$ were underpredicted (-20%). Hypothesis (3) showed increased CL_{TAM} estimates with earlier assumption of st-st. Thus, simulations with the re-estimated parameter sets with early st-st assumption (day 5) displayed decreased $C_{ss,TAM}$ (-30%) and even lower $C_{ss,ENDX}$ (-50%) compared to the reference.

Conclusions: None of the three hypotheses per se were able to capture both the predictions of TAM and ENDX for M2. The differences in model predictions might be due to a combination of the hypothesised factors, rather than explained by one factor alone, or additional factors. This simulation exercise exemplifies that factors such as st-st assumption, differences in F or adherence have a considerable impact on model predictions of TAM and ENDX emphasising the need to account for them in clinical trials, clinical practice and data analysis.

References:

[1] Dahmane EBA. Tamoxifen Pharmacokinetics and Pharmacogenetics in Endocrine Sensitive Breast Cancer Patients. Thèse de doctorat: Univ. Genève (2013) no. Sc. 4617.

[2] Ter Heine R et al. Population pharmacokinetic modelling to assess the impact of CYP2D6 and CYP3A metabolic phenotypes on the pharmacokinetics of tamoxifen and endoxifen. Brit J Clin

Pharmacol (2014) 78(3): 572–86.
[3] Klopp-Schulze L et al. In silico simulation study : A comparison of two population pharmacokinetic models of tamoxifen and its major metabolite endoxifen. PAGE 24 (2015) Abstr. 3447 [www.page-meeting.org/default.asp?abstract=3447]

I-64: *Katrine Knøsgaard* A model-based approach for joint analysis of pain intensity and opioid consumption in postoperative pain

Katrine R Knøsgaard, M.Sc. (1), Rasmus V Juul, M.Sc. (1), Anne E Olesen, Ph.D. (1,2), Katja V Pedersen, Ph.D. (3,4), Mads Kreilgaard, Ph.D. (1), Lona L Christrup, Ph.D. (1), Palle J Osther M.D.; Ph.D. (3), Asbjørn M Drewes, M.D., Ph.D. (2), Trine M Lund,
(1) Department of Drug Design and Pharmacology, University of Copenhagen, Denmark 2) Mech-Sense, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Denmark 3) Urological Research Center, Lillebaelt Hospital, University of Southern Denmark, Fredericia, Denmark 4) Department of Clinical Genetics, Odense University Hospital, Denmark

Objectives: Joint analysis of pain intensity and opioid consumption is encouraged in trials of postoperative pain [1]. However, previous approaches have not appropriately addressed the complexity of their interrelation in time [2,3]. We hypothesized that adequate joint data analysis of pain intensity and opioid consumption required description of four key phases: A) pain intensity in time, B) probability of threshold pain, C) probability of opioid request and D) opioid effects on pain intensity. It was the aim of this study to demonstrate the application of a joint analysis approach spanning the four key phases using non-linear mixed effects modeling.

Methods: In this study we applied a non-linear mixed effects model to simultaneously study pain intensity and opioid consumption in a 4-hour postoperative period for 44 patients undergoing percutaneous kidney stone surgery. Analysis was based on 748 numerical rating scores (NRS) of pain intensity and 51 observed morphine and oxycodone dosing events.

Results: A joint model was developed to describe the recurrent pattern of four key phases determining the development of pain intensity and opioid consumption in time; A) Distribution of pain intensity scores which followed a truncated Poisson distribution with time-dependent mean score ranging from 0.93 to 2.45; B) Probability of transition to threshold pain levels (NRS≥3) which was strongly dependent on previous pain levels ranging from 2.8-15.2% after NRS of 0-2; C) Probability of requesting opioid when allowed (NRS≥3) which was strongly correlated with the number of previous doses, ranging from 89.8% for requesting the first dose to 26.1% after three previous doses; D) Reduction in pain scores after opioid dosing which was significantly related to the pain intensity at time of opioid request ($p<0.001$). This study highlights the importance of analyzing pain intensity and opioid consumption in an integrated manner.

Conclusions: Non-linear mixed effects modelling proved a valuable tool for analysis of interventions that affect pain intensity, probability of rescue dosing or the effect of opioids in the postoperative pain period.

References:
[1] US Food Drug Administration. Guidance for industry analgesic indications: developing drug and biological products., 2014
[2] McQuay HJ, Derry S, Eccleston C, Wiffen PJ, Andrew Moore R. Evidence for analgesic effect in acute pain - 50 years on. Pain 2012;153(7):1364-1367.
[2] Woolf CJ. Overcoming obstacles to developing new analgesics. Nature medicine 2010;16(11):1241-1247.

I-65: *Gilbert Koch* Facilitate treatment adjustment after accidental overdosing: pharmacometric modelling to support clinical practice

Gilbert Koch (1), Johannes Schropp (2), Marc Pfister (1)
(1) Paediatric Pharmacology and Pharmacometrics Research Centre, University of Basel, Children's Hospital (UKBB), Basel, Switzerland (2) Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany

Objectives: Accidental once or repeated overdosing is a frequent and potentially fatal clinical situation affecting paediatric and adult patients [1],[2]. A critical question after a period of overdosing is to understand the time it will take for the drug concentration to return to the target range associated with correct reference dose. We developed a method that calculates the optimal waiting time between a period of overdosing and the next reference dose to ensure safe and efficacious treatment.

Methods: A general mathematical framework was developed to calculate the waiting time after overdosing until the next correct therapeutic dose can be administered. We related the drug concentration after last overdose to the target range characterized by the steady state concentration with the reference dosing. The resulting equation is then solved to compute the waiting time.

Results: For simplicity our method was applied to a one-compartment model and intravenous drug administration. The mathematical solution permits to calculate the waiting time between the last overdosing and the next therapeutic dose based on half-life of a given drug. The approach calculates the waiting time independently of the volume of distribution, a major advantage as this parameter is usually not known in clinical practice. Two real-life overdosing scenarios are presented. First, we investigate a tenfold amikacin overdose in a one day old preterm neonate. Second, we analyse multiple overdosing of vancomycin over an entire week in an infant with undiagnosed impairment of kidney function. An online available Time to Next Dose (TND) calculator was developed to support clinicians who care for optimized treatment adjustment after overdosing.

Conclusions: This is the first quantitative approach to assess the waiting time after accidental overdosing to ensure safe and efficacious continuation of necessary treatment. The presented work is another step to bridge the gap between pharmacometric modelling and application of precision medicine in clinical practice. The developed online TND decision support tool helps clinicians to efficiently adjust treatment after accidental overdosing benefiting paediatric and adult patients.

References:
[1] Ghaleb MA et al. (2010) The incidence and nature of prescribing and medication administration errors in paediatric inpatients, Arch Dis Child 95:113-18
[2] Lewis PJ et al. (2009) Prevalence, incidence and nature of prescribing errors in hospital inpatients, Drug Safety 32(5):379-89

I-66: *Anders Kristoffersson* Design and Interim Evaluation of a Sparse Sampling Schedule for Estimation of Individual Colistin Pharmacokinetics

Anders N Kristoffersson and Lena E Friberg
Department of Pharmaceutical Biosciences, Uppsala University

Objectives: As part of the EU funded AIDA project a multicenter, open-label, randomized 360 patient clinical trial (180 patients in each arm) has been initiated with the aim to compare colistin alone vs. colistin plus meropenem against severe infections caused by carbapenem-resistant bacteria [1]. The aim of this work was to propose a sparse sampling pharmacokinetic (PK) schedule for colistin and its prodrug CMS by application of optimal design (OD) methodology and to make an interim analysis from the study data to evaluate the design.

Methods: The CMS dosing schedule was a 9 MU loading dose, and a 4.5 MU twice daily maintenance dose given as 30 min infusions. The two sampling points were optimized for individual exposure determination of colistin in PopED [2] using the MAP_{occ} [3] method to handle inter occasion variability (IOV) present in the PK model [4], with sampling allowed 15 min post end of infusion and until the start of the next infusion. Samples from the first 98 included patients have been assayed and were used to evaluate the design based on precision and distribution shrinkage (SH) of the individual parameter estimates as reported by NONMEM [5].

Results: The optimal sampling times were found to be at 45 min and 10 h post start of first and second of infusions respectively, and predicted to give satisfactory precision and SH in the most important colistin exposure determinant, the individual apparent clearance (CL/fm) estimate. Twenty-six of the patients adhered to the optimal sampling protocol while 44 entered the study after initiation of colistin treatment and the remaining 28 did not conform to the sampling schedule. The precision and SH in the individual CL estimate was best for the group entering the study after initiation of treatment, but was satisfactory for all groups (reduction in uncertainty vs. the population variability by >39% and a SH <30%).

Conclusions: An optimized PK sampling schedule was developed and found to result in individual CL estimates with low SH. The result brings confidence for the ability to evaluate covariates that may affect CL as well the relationship between colistin exposure and microbiological and clinical outcomes. Analysis is ongoing of the remaining patients and a full report including covariate data is intended to be submitted at the end of the year.

Acknowledgments: This project was funded by the EU-project AIDA (grant Health-F3-2011-278348) to LEF

References:

[1] Y. Dickstein, L. Leibovici, D. Yahav, N. Elyakim-Raz, G.L. Daikos, A. Skiada, A. Antoniadou, Y. Carmeli, A. Nutman, I. Levi, A. Adler, E. Durante-Mangoni, R. Andini, G. Cavezza, J.W. Mouton, R.A. Wijma, U. Theuretzbacher, L.E. Friberg, A.N. Kristoffersson, O. Zusman, F. Kopel, Y. Dishon, S. Altunin, M. Paul, and the AIDA consortium. Multicenter open-label randomized controlled trial to compare colistin alone with colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative infections (AIDA): study protocol. BMJ Open (*in press* 2016).
[2] J. Nyberg, S. Ueckert, E.A. Stromberg, S. Hennig, M.O. Karlsson, and A.C. Hooker. PopED: an extended, parallelized, nonlinear mixed effects models optimal design tool. Comput Methods Programs Biomed. 108:789-805 (2012).

[3] A. Kristoffersson, L. Friberg, and J. Nyberg. Inter occasion variability in individual optimal design. Journal of Pharmacokinetics and Pharmacodynamics. 42:735-750 (2015).
[4] A.F. Mohamed, I. Karaiskos, D. Plachouras, M. Karvanen, K. Pontikis, B. Jansson, E. Papadomichelakis, A. Antoniadou, H. Giamarellou, A. Armaganidis, O. Cars, and L.E. Friberg. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother. 56:4241-4249 (2012).
[5] R.B. Bauer. NONMEM users guide. Introduction to NONMEM 7, ICON Development Solutions, Elicott City, Maryland, 2010.

I-67: *Anne Kuemmel* PECAN, a Shiny application for calculating confidence and prediction intervals for pharmacokinetic and pharmacodynamic models

Anne Kümmel (1), Ahmad Abu Helwa (2), Andreas Krause (1)
(1) Department of Clinical Pharmacology, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland (2) Australian Centre for Pharmacometrics and Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Australia

Objectives: Estimation accuracy for PK/PD or dose response models is typically reported as standard errors of the model parameters. However, for judging the uncertainty of predicted clinical outcomes, e.g., the clinical benefit of an untested dose, standard errors and confidence intervals around the regression fit are of higher relevance. PECAN, an R-based application with a Shiny interface, provides calculation and visualization of confidence and prediction intervals for PK and PK/PD models.

Methods: The PECAN interface enables data upload and model selection, parameter estimation and confidence calculation of the predictions. For parameter estimation, either non-linear least squares or maximum likelihood estimation (MLE) is used. For MLE, additive, proportional, a combination of additive and proportional and an exponential error model is applied. Confidence intervals are calculated using either the δ-method [1], by sampling from the parameter covariance matrix, by bootstrapping, or by Monte-Carlo-simulations [2, 3]. Compartmental PK models amongst others based on ADVAN-style implementation [4] and PK/PD models are included in the PECAN's model library. The PECAN interface visualizes the uploaded data. After parameter estimation, estimation results and diagnostic plots are shown. Finally, the model prediction, its confidence and prediction intervals and the data are overlaid enabling a visual check of the model fit and its uncertainty and variability.

Results: PECAN combines models for pharmacometric applications and different methods into a single user interface, generalizing the idea of confidence and prediction intervals. PECAN demonstrates how PK and PK/PD model uncertainty can be derived in a standard programming language such as R. At the same time, the implementation as a Shiny application provides easy access for a broad audience. The user can choose between different methods for estimation and confidence calculation and error models. The Shiny application can be accessed at https://carumcarvi.shinyapps.io/pecan/

Conclusions: Visualization of model fit, confidence and prediction intervals allows judgment about the overall uncertainty of PK and PK/PD models: the uncertainty around the fitted model curve in contrast to only the individual model parameter estimates. This allows a direct visual assessment of the predicted relevant clinical outcome, e.g., the expected response of a future dose or the PK profile.

References:

[1] Hosmer, D.W., S. Lemeshow, and M. S., Applied Survival Analysis: Modeling of Time-to-Event Data. 2011, John Wiley and Sons, Inc.
[4] Abuhelwa, A.Y., D.J. Foster, and R.N. Upton, ADVAN-style analytical solutions for common pharmacokinetic models. J Pharmacol Toxicol Methods 73 2015; 42-8.
[2] Bonate, P.L., Pharmacokinetic-pharmacodynamic modeling and simulation. 2011, New York: Springer.
[3] Lavielle, M., Mixed effects models for the population approach: Models, tasks, methods and tools. 2014: Chapman and Hall/CRC.
[4] Abuhelwa, A.Y., D.J. Foster, and R.N. Upton, ADVAN-style analytical solutions for common pharmacokinetic models. J Pharmacol Toxicol Methods 73 2015; 42-8.

I-68: *Manish Kumar* Elucidating metabolic variations in gut microbiota during health and malnutrition based on genome scale metabolic modeling approach

Manish Kumar, Boyang Ji, Parizad Babaei, Jun Geng, Adil Mardinogulu, & Jens Nielsen*, representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community
Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden

Objectives: Recent metagenomics studies have shown strong associations between the alteration of gut microbiota and children malnutrition [1,2]. However, precise mechanisms governing metabolic transition in the gut stimulated by the intestinal microbiota during health and malnutrition is unclear. Genome-scale metabolic reconstructions and their analysis with constraint-based modeling techniques are natural next steps after sequencing of a genome to link top-down systems biology analyses at genome scale with bottom-up systems biology modeling. In this study, we have employed genome scale metabolic modeling to understand the metabolic variations in gut microbiota of children during health and malnutrition.

Methods: To quantify the contribution of gut microbiota to the metabolic differences between health and malnutrition of children, we have reconstructed genome scale metabolic models (GEMs) for 52 species, which represent the 20 most abundant species in the gut microbiota of malnourished (Bangladeshi and Malawi) and healthy (Swedish, Bangladeshi, and Malawi) children [1–3]. With these GEMs, we inferred the metabolic signatures of the most abundant gut bacterial species, which provide the basis for analysis of gut microbial communities by metabolic modeling.

Results: Simulation of these GEMs based on single species allows to quantify the production capabilities of gut bacteria towards synthesis of beneficial small molecules such as short chain fatty acids (SCFAs) and amino acids (AAs). Results demonstrate that variations in synthesis of small molecules are directly connected to changes in gut microbiota composition between healthy and malnourished children. Focusing on the effects of food interventions on gut microbiota and host metabolism, we found transient effects of standard Ready-To-Use-Food treatment to gut microbiome.

Conclusions: Results of this study suggested that the gut microbiota in Bangladeshi and Malawian children is less diverse than Swedish cohort. There is only a slight difference in production of SCFAs and AAs between healthy and malnourished Bangladeshi children. For Malawian children there seems to be no metabolic difference between healthy and malnourished children, which could point to an effect of vitamins and/or minerals. The metabolic diversity of both Malawian and Bangladeshi children is much lower than in Swedish children, which may point to a problem with lack of microbiota diversity connected to malnutrition.
#This work is sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative.

References:
[1] Smith, M. I. et al. Gut Microbiomes of Malawian Twin Pairs Discordant for Kwashiorkor. Science (80-.). 339, 548–554 (2013).
[2] Subramanian, S. et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature 29–31 (2014). doi:10.1038/nature13421
[3] Bäckhed, F. et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. Cell Host Microbe 17, 690–703 (2015).

I-69: *Max Lagraauw* A population disease progression model for Amyotrophic Lateral Sclerosis – Results of the Treeway Summer Challenge 2015

Melanie Titze (1), Annemijn Jonkman (1), Magnus Munch (1), H. Maxime Lagraauw (1,2), Piet H. van der Graaf (2), Bernard Muller (1), Inez de Greef (1)
(1) Treeway B.V., Tilburg, The Netherlands; (2) Systems Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Background: Amyotrophic lateral sclerosis (ALS) is a progressive and deadly motor neurone disease, in which the motor neurons innervating skeletal muscle degenerate. World-wide it affects around 400.000 patients and their families. The average life expectancy upon diagnosis with ALS is only 3-5 years, during which muscle function gradually declines and eventually leads to respiratory dysfunction and death. Progression of the disease is monitored by means of the ALS Functional Rating Scale (ALSFRS), evaluating the ability to perform several physical tasks. However, disease progression, as assessed by this symptomatic scale, is highly variable between patients, thus complicating accurate estimation of patient's prognosis and clinical trial design.

Objectives: During the 10-week Treeway Summer Challenge 2015, a group of 9 MSc. and PhD students aimed to gain more insight in the complex pathobiology of ALS and to develop a disease progression model to better understand patient heterogeneity and predict disease progression on population and individual level.

Methods: Longitudinal ALSFRS scoring data was obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. Patients from both active and placebo treatment arms, but not those on riluzole, were included. Using these criteria data from 1065 ALS patients and a total of 8174 ALSFRS evaluations were available for the fitting of the longitudinal disease progression model.

Results: Similar to the only available ALS disease progression model in literature [1], disease progression was best described by the Weibull function. Subsequent stepwise covariate model building resulted in the inclusion of baseline ALSFRS (BAS) on all three function parameters and site of onset as a covariate on the time-dependent parameter (td). With this model the occurrence of two distinct subpopulations could be explained by the site of onset: bulbar- vs. limb-onset.

Conclusions: The current model provided an adequate model to describe the longitudinal disease progression as measured by the ALSFRS score and could distinguish two subpopulations with distinct disease progression rates based on site of onset. Still, there remains a high degree of interindividual variability which should be explored in further research.

References:
[1] Gomeni R, Fava M, PRO-ACT Consortium. Amyotrophic lateral sclerosis disease progression model. Amyotroph Lateral Scler Front Degener. 2014 Mar 1;15(1-2):119–29.

I-70: *Laure Lalande* Mathematical modeling and systems pharmacology of tuberculosis therapy with isoniazid

Laure Lalande (1), Laurent Bourguignon (1,2,3), Pascal Maire (1,2), Sylvain Goutelle (1,2,3)
(1) Université Lyon 1, CNRS, UMR5558, Laboratoire de Biométrie et Biologie Evolutive, Villeurbanne, France. (2) Service Pharmacie, Groupement Hospitalier de Gériatrie, Hospices Civils de Lyon, Lyon, France. (3) Université Lyon 1, ISPB – Faculté de Pharmacie, Lyon, France.

Objectives: To develop a mathematical model describing the time-course of tuberculosis infection and its early treatment by isoniazid (INH) in the human lung. Then, to simulate the antibacterial effect of various INH dosage regimens and explore the drug and host determinants of the killing effect of INH against *Mycobacterium tuberculosis* (MTB).

Methods: We combined a pharmacokinetic (PK) model describing the plasma and lung disposition of INH in human [1], a pharmacodynamic (PD) model describing the relationship between INH concentration and its antibacterial effect [2], and an immune response model [3] to build a full systems' pharmacology model of TB treatment by INH. This model was used to simulate various INH dosing therapy. The antibacterial effect on extracellular MTB predicted over the first days of therapy was compared to published values of early bactericidal activity (EBA). Global sensitivity analysis was performed using GUI-HDMR software tool to identify the model parameters that mostly influenced the early effect [4].

Results: For the standard INH dose of 300 mg/day, the predicted EBAs for the first two days of therapy were 0.454 ± 0.272 and 0.594 ± 0.243 $\log_{10}$CFU/mL/day, for fast and slow acetylators respectively. These values were in accordance with values of EBA reported in patients as they ranged between 0.371 and 0.770 $\log_{10}$CFU/mL/day [5]. Importantly, the model reproduced features of the antibacterial effect of INH observed in humans: the early antibacterial effect of INH appeared to level off for doses above 300 mg, and the killing effect displayed the typical biphasic shape of INH effect. The global sensitivity analysis revealed that the early antibacterial effect of INH was mostly influenced by PK and PD parameters such as plasma elimination rate constant, rate transfer from plasma to the lung, and maximal killing effect. However, an influence of pathophysiological parameters, although limited, appeared during the second phase of the decline.

Conclusions: Our model qualitatively and quantitatively reproduced important characteristics of the antibacterial effect of INH observed in patients. Simulations indicated that INH early killing effect was largely influenced by PK variability. This model framework may be extended to other anti-TB drugs and may be useful for preclinical development of anti-TB drug regimens.

References:

[1] Lalande, L., Bourguignon, L., Bihari, S., Maire, P., Neely, M., Jelliffe, R., Goutelle, S., 2015. Population Modeling and Simulation Study of the Pharmacokinetics and Antituberculosis Pharmacodynamics of Isoniazid in Lungs. Antimicrob. Agents Chemother. 59, 5181–5189.
[2] Gumbo, T., Louie, A., Liu, W., Ambrose, P.G., Bhavnani, S.M., Brown, D., Drusano, G.L., 2007. Isoniazid's bactericidal activity ceases because of the emergence of resistance, not depletion of Mycobacterium tuberculosis in the log phase of growth. J. Infect. Dis. 195, 194–201.
[3] Marino, S., Kirschner, D.E., 2004. The human immune response to Mycobacterium tuberculosis in lung and lymph node. J. Theor. Biol. 227, 463–486.
[4] Ziehn, T., Tomlin, A.S., 2009. GUI–HDMR – A software tool for global sensitivity analysis of complex

models. Environ. Model. Softw. 24, 775–785.
[5] Donald, P.R., Diacon, A.H., 2008. The early bactericidal activity of anti-tuberculosis drugs: a literature review. Tuberc. Edinb. Scotl. 88 Suppl 1, S75–83.

I-71: *Silvia Maria Lavezzi* Structural and practical identifiability of some mPBPK-TMDD models

Lavezzi Silvia Maria (1), Zamuner Stefano (2), De Nicolao Giuseppe (1), Ma Peiming (3), Simeoni Monica (2)
(1) Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy, (2) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, UK, (3) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, China

Objectives: In model building the study of structural (a priori) and practical (a posteriori) identifiability is a crucial step. A priori identifiability is a necessary but not sufficient condition for a posteriori identifiability [1]. In [2], four mPBPK-TMDD models (Full, A, A+B and A+B+C, including up to 3 quasi-steady-state approximations) have been presented and compared, detecting practical identifiability issues on the basis of preliminary fitting tests. The aims of the present work are to verify whether such identifiability issues originated from the lack of structural identifiability and investigate via a Monte Carlo (MC) approach the influence of noise on parameter estimates.

Methods: A local a priori identifiability analysis of the models was carried out via the Identifiability Analysis package [3,4]. Since this tool requires the model to be rational [3], the models were rationalized by adding a dummy state whenever needed. Availability of the following output measures was assumed: i) plasma drug concentration, ii) drug concentration both in plasma and in binding tissue, iii) plasma drug concentration together with target concentration in binding tissue. The input is an i.v. bolus of 1 or 5 mg/kg.
The steps of MC a posteriori identifiability analysis were: simulation of different datasets in R 3.1.2, identification of the models in NONMEM 7.3, study of the distribution of estimates and concentration profiles.

Results: A priori identifiability could be assessed in three models. Full Model and Model A were found to be a priori identifiable for every output choice (i,ii,iii). Model A+B is a priori identifiable only with the output choice iii); in cases i) and ii) kdeg and kss are the non-identifiable parameters. As for MC analysis, conditional weighted residuals and goodness of fit plots did not show any significant trend; a ranking of the parameters based on RMSE quantified the sensitivity of parameter estimates to noise in the data, with some CV% exceeding 150.

Conclusions: A priori and a posteriori identifiability of four mPBPK-TMDD models [2] were investigated. For the Full Model and Model A, it was found that practical identifiability issues previously detected are not due to a lack of structural identifiability. The MC analysis confirms that all the four models have practical identifiability issues. Further development may concern the potential benefits ensuing from adopting optimal design methods.

References:
[1] *Structural Identifiability of Systems Biology Models: A Critical Comparison of Methods*. O.-T. Chis, J.R. Banga, E. Balsa-Canto. PLoS ONE, 6 (11), 1-16, 2011.
[2] *Integrating Target Mediated Drug Disposition (TMDD) into a minimal physiologically based modelling framework: evaluation of different quasi-steady-state approximations*. E. Mezzalana, S.M. Lavezzi, S. Zamuner, G. De Nicolao, P. Ma, M. Simeoni. PAGE 24 (2015) Abstr 3598
[3] *An Efficient Method for Structural Identifiability Analysis of Large Dynamic Systems*. J. Karlsson, M. Anguelova, M. Jirstrand. 16th IFAC Symposium on System Identification, 16 (1), 941-946, 2012.

[4] *Minimal output sets for identifiability*. M. Anguelova, J. Karlsson, M. Jirstrand. Math Biosci, 239, 139-153, 2012

I-72: *Jean Lavigne* Modeling and simulation of smear count after administration of Eurartesim® (piperaquine (PQ) tetraphosphate/dihydroartemisinin (DHA)) in infected patients with Plasmodium falciparum malaria

Jean Lavigne (1), Mary Lor (1), and Silvia Pace (2)
(1) Celerion, Montreal, Canada, (2) Sigma-Tau, Rome, Italy

Objectives: Develop a population pharmacokinetic and pharmacodynamic (PK/PD) model for the treatment and smear count of Plasmodium falciparum by pooling data from 5 studies (PK part), 2 patients studies (PD part), and applying them to predict the smear count in pediatric patients (6-12 months) infected with P. falciparum malaria after administration of a new dispersible formulation.

Methods: PK parameters for both drugs were developed[1,2] and the Bayesian estimates were fixed. The patients with Bayesian estimated PK parameters from both medications were included in the analysis for a total of 50 smear count profiles, 563 samples (163 were greater than zero). The MLEM algorithm in ADAPT5[3] was used to estimate the population PD parameters. The natural logarithm of the smear count plus two was used for PD modeling. The initial conditions were fixed to the measure smear level before administration of the medication. The covariates age, body weight (WGT), body surface area, sex, race (RACE), fasted/fed, and crushed/not crushed were explored. The Bayesian Information Criteria (BIC) was used for model discrimination and covariate inclusion/exclusion.

Results: A one-compartment model with a grow and kill rate based on both medications best fitted the smear count data. An antagonistic effect was assumed between the two medications[4], i.e., less than additive, the worst case scenario was achieved by taking the kill rate to be the maximum effect for the two medications. DHA and PQ effects were modeled with an Emax and a sigmoidal Emax model, respectively. An onset of effect parameter and the inclusion of RACE on DHAmax both improved the BIC. It was suspected that RACE was more a marker of different parasite populations since one study was conducted in Asia with Asian adult patients and the second study was conducted in Africa with Black pediatric patients. The model estimated a 48-hour parasite growth rate in blood to be 18.3, which was within the range reported in the literature[5]. For the simulations, WGT was simulated according to the WHO training[6]. One thousand Black infants were simulated receiving 80/10, 160/20, or 320/40 mg PQ/DHA depending of their WGT once a day for 3 consecutive days. The simulated results suggested a geometric mean parasite clearance time of 22.5 hours (range between 10 to 65 hours).

Conclusions: The model described well the parasite smear level count and the geometric mean parasite clearance time of 22.5 hours.

References:

[1] Lavigne J., Lor M., Pace S. Modeling and Simulation of Piperaquine (PQ) after Administration of Eurartesim® (PQ Tetraphosphate/Dihydroartemisinin). Poster presented at ACoP2015 (http://celerion.com/wordpress/wp-content/uploads/2015/10/Celerion_2015-ACOP_Modeling-and-Simulation-of-Piperaquine-PQ-after-Administration-of-Eurartesim.pdf).
[2] Lavigne J., Lor M., Pace S. Modeling and Simulation of Dihydroartemisinin (DHA) after Administration of Eurartesim® (Piperaquine Tetraphosphate/DHA). Poster presented at PAGE2014 (http://www.page-meeting.org/pdf_assets/5485-14_05%20PAGE%20pst%20D5.pdf).
[3] D'Argenio, D.Z., A. Schumitzky and X. Wang. ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Biomedical Simulations Resource, Los Angeles, 2009.

[4] Anirudh Gautam, Tausif Ahmed, Vijay Batra and Jyoti Paliwal Pharmacokinetics and Pharmacodynamics of Endoperoxide Antimalarials, Current Drug Metabolism, 2009, 10, 289-306
[5] Philip Bejon, Laura Andrews, Rikke F Andersen, Suzanna Dunachie, Daniel Webster, Michael Walther, Sarah C. Gilbert, Tim Peto, and Adrian V. S. Hill. Calculation of Liver-to-Blood Inocula, Parasite Growth Rates, and Preerythrocytic Vaccine Efficacy, from Serial Quantitative Polymerase Chain Reaction Studies of Volunteers Challenged with Malaria Sporozoites. The Journal of Infectious Diseases, 2005; 191:619-26. (https://jid.oxfordjournals.org/content/191/4/619.full)
[6] Training Course on Child Growth Assessment – WHO – Module C: Interpreting Growth Indicators. (http://www.who.int/childgrowth/training/module_c_interpreting_indicators.pdf)

I-73: *Mary Lavy* Population Pharmacokinetics (PK) and Pharmacodynamics (PD) of Natalizumab in Patients with Multiple Sclerosis (MS)

Kumar Kandadi (1), Ivan Nestorov (1), Geoffrey Kuesters (2), Meena Subramanyam (2), Tatiana Plavina (2)
(1) Systems Pharmacology, Biogen, Cambridge, MA, USA. (2) Translational Sciences, Biogen, Cambridge, MA, USA.

Objectives: Natalizumab is a first-in-class, humanized anti-α4 integrin antibody used to treat MS. Currently, no robust quantitative models describe the PK of natalizumab and the natalizumab concentration-α4 integrin saturation relationship. The objective of this analysis is to develop a population PK and PD model to characterize natalizumab PK and α4 integrin saturation (PD) across MS subjects with intravenous (IV) natalizumab administration.

Methods: The natalizumab serum PK and α4 integrin saturation PD data were obtained across 2 phase 2, 3 phase 3, and 5 postmarketing clinical studies. In total, 12788 serum and 4917 α4 integrin samples from 12788 patients were included in the population analysis. PK and PD models were developed sequentially using NONMEM (version 7.3). Diagnostics plots and various predictive check procedures were used for model evaluation.

Results: Natalizumab PK was best described by a 2-compartmental model with linear and Michaelis-Menten elimination. Based on the model, the median (95% confidence interval) linear clearance (CL) is 6.21 mL/h (5.60-6.70), median volume of distribution at steady state (V_{ss}) is 5.58 L (5.27-5.92), and terminal elimination half-life ($t_{1/2,\beta}$) is 26.8 days. 90% of steady state concentrations were expected to be reached by 5-7 months for an individual dosed with 300 mg Q4W (every 4 weeks) IV natalizumab. Covariate analysis showed that CL, V_1 (central volume of distribution) increased as body weight increased. CL was higher in subjects who were administered with phase 2B formulations relative to commercial formulations and in those who developed binding antibodies to natalizumab. The relationship between natalizumab concentration and α4 integrin saturation was best described by a direct response model with a sigmoidal effect on α4 integrin saturation mediated by an Emax relationship with natalizumab concentrations. The model-estimated Emax and EC50 were 83.8% and 2.51 mg/L, respectively. The magnitude of PD response as measured by Emax and Hill coefficient was affected by administered natalizumab formulation and subject age.

Conclusions: The population PK-PD model adequately characterized natalizumab PK-PD in MS subjects. The nonspecific disposition component (CL, V_{SS}) estimates were consistent with results obtained for other IgG monoclonal antibodies [1]. The PK-PD covariates, although statistically significant, are not expected to have any clinical impact at the approved clinical dosing regimen (300 mg Q4W).

References:

[1] Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010;49(10):633-59.

I-74: *Robert Leary* An Improved Framework for Shrinkage Computations in NLME Population Models

Robert H. Leary (1), Michael Dunlavey (1), Kevin Feng (1), Shuhua Hu (1)
(1) Certara/Pharsight

Objectives: Shrinkage evaluation is based on comparing the variance over subjects of empirical Bayesian estimates (EBEs) of a random effect ETA(I) to the corresponding parameter OMEGA(I,I). ETA shrinkage refers to the fact this variance is smaller than OMEGA(I,I), while EPS shrinkage refers to the variance of residuals evaluated at ETAs set equal to EBE values being smaller than the corresponding residual error parameter [1]. The most common form of EBE in current use is the mode (MAP estimate) of the empirical Bayesian distribution (EBD) which is the central focus of any conditional method such as FOCEI. However, in EM-based methods, the mean rather than the mode of the EBD plays the central role. We investigate the properties of EBD mean- vs mode-based shrinkages.

Methods: The methods used to derive the properties of EBD mean-based shrinkages are based both on a)theoretical analysis of the fixed point conditions that hold at convergence of EM methods and b) numerical examples of mode- vs mean-based shrinkages based on applying the ELS FOCE, QRPEM, and nonparametric algorithms in Phoenix NLME™ to several simulated models.

Results:

a)The results in [2] are claimed by the authors to suggest that “on average, there is a 1:1 relationship” between shrinkage and relative estimation error for EBEs of PK parameters. In fact, this relationship becomes an easily provable theorem in the mean-based case.

b)In the mean-based case, there is a relationship between EPS shrinkage and the ETA shrinkages which can be used to assign the relative amounts of intra- and inter-individual variability. In the special case of homoscedastic linear models, this amounts to an exact division of the total degrees of freedom (number of observations) into EPS and ETA related parts.

c) Mean based shrinkage calculations can easily and naturally be extended to nonparametric population modeling.

d) The linear regression used in EM methods to update covariate parameters is based on response variables defined by the EBD means. Thus we may expect investigation of prospective linear covariate relationships to be more informative, particularly in the high shrinkage case, than using responses based on EBD modes. This in fact is born out in several test examples..

Conclusions: Shrinkage computations based on means rather than modes of the EBD are more amenable to exact theoretical analysis and additionally offer practical advantages.

References:
[1] Savic RM, Karlsson MO. Importance of shrinkage in empirical Bayes estimates for diagnostics:problems and solutions. AAPS J. 2009; 11(3):558-69.
[2] Xu SX, Yuan M, Karlsson MO, Dunne A, Nandy P, Vermeulen A. Shrinkage in nonlinear mixed effects population models: quantification, influencing factors and impact. AAPS J. 2012; 14(4):927-36.

II-01: *Khaled Abduljalil* Simcyp Simulator within the DDMoRe Interoperability Framework – Proof of Concept Cases

Khaled Abduljalil, Craig Lewin, Adrian Barnett, Steve Marciniak, Masoud Jamei
Simcyp Limited (a Certara company)

Objectives: A corner stone of model-informed drug development is interoperability among various models, tools and platforms. The Drug Disease Model Resources (DDMoRe) consortium aims at establishing such a framework. As part of this initiative the Simcyp population based physiologically-based pharmacokinetic and pharmacodynamics (PBPK/PD) platform has been further developed and bundled with a command line console which adds support for the DDMoRe Interoperability Framework. In this work two proof of concept case studies are presented.

Methods: Case 1: The Model Description Language Integrated Development Environment (MDL-IDE) was used together with leveraging Simcyp-specific functions within the DDMoRe R package to generate a population data with different CYP2D6 phenotypes as well as PBPK profiles for metoprolol using Simcyp Simulator V15. These data were in the form of a Standard Output (SO) file and numerous Comma Separated Values (CSV) files which were parsed by an R script within the MDL-IDE. The data were then used to construct a table containing dosing, covariates and concentration profiles and passed within mdl file to NONMEM.

Case 2: The MDL-IDE was used to create and execute an R script which utilised functions within the Simcyp R package to execute a pre-saved Simcyp workspace for full PBPK model of midazolam after i.v. administration to paediatric and adult populations. The simulated concentration and PK parameters for both populations were retrieved using Simcyp R package and compared.

Results: While the DDMoRe interoperability framework support is still a 'work in progress', capabilities of the Simcyp Simulator were successfully used from within the MDL-IDE to produce population, compound, and trial design data in the form of a SO file. This was achieved through the use of new Simcyp features, including; the Simcyp R package, Simcyp functions within the DDMoRe R package, and the Simcyp Console application. The obtained PK profiles and database can be submitted for additional tasks within the DDMoRe interoperability framework.

Conclusion: The unique functionality within Simcyp Simulator V15 will allow DDMoRe partners with a Simcyp Simulator licence to run simulations and generate populations in scripted workflows with other software such as NONMEM, Monolix, PFIM, and PopED. The new features may be used independently of DDMoRe facilities and users will benefit from the Simulator’s vast databases of populations, compounds and PBPK/PD models.

II-02: *João Abrantes* Population pharmacokinetic analysis of factor VIII activity following treatment with moroctocog alfa in moderate to severe haemophilia A subjects

João A Abrantes (1), Elisabet I Nielsen (1), Joan Korth-Bradley (2), Lutz Harnisch (3), Siv Jönsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) Pfizer Inc, Collegeville, Pennsylvania, USA, (3) Global Clinical Pharmacology, Pfizer, Sandwich, UK

Objectives: Moroctocog alfa is a B-domain deleted recombinant factor VIII (FVIII) indicated for the treatment and prophylaxis of bleeding in adults and children with haemophilia A. The aim of this study is to develop a population pharmacokinetic model of FVIII activity following moroctocog alfa treatment in moderate to severe haemophilia A patients using all available clinical study data.

Methods: A population pharmacokinetic model (NONMEM 7.3) was developed with data from 13 trials involving IV administration of moroctocog alfa products (Refacto®, Refacto AF®, Xyntha® Wyeth Pharmaceuticals Inc. [Pfizer], Philadelphia, USA). The studies were conducted from 1993 to 2013 in 25 countries, and included rich sampling (≥10 samples post-dose, n=4), sparse sampling (2-3 samples per occasion, n=5) or both (n=4). The influence of age, measures of body size, race, ethnicity, inhibitor status and titre, assay, year of study, study and country, were investigated. Data below the lower limit of quantification were handled using the M3 method [1] and correlated residual errors for repeated analyses were accounted for by using the L2 data item [2].

Results: A total of 259 children and 497 adults with moderate to severe haemophilia A (FVIII ≤5 IU/dL) were included in the analysis. Age ranged from 1 day to 73 years and weight from 3 to 134 kg. Missing height data (37% of the cases) was imputed using a function charactering the relationship between height and weight in the remaining population. A two-compartment model with allometrically scaled weight on disposition parameters was found to adequately describe the combined data. Pre-dose activity observations were described by estimating an endogenous FVIII activity at 0.0012 IU/mL together with an additive component accounting for residual activity from previous unknown doses (0.023 IU/mL at time 0, declining over time in line with FVIII disposition). For a typical 68-kg, 23-year-old patient with severe haemophilia A, FVIII activity clearance was estimated at 281 mL/h, central volume of distribution at 2.7 L, peripheral volume of distribution at 1.5 L, and inter-compartmental clearance at 3090 mL/h.

Conclusions: The model may be an aid in dose individualization, when used with patient observations, with the ultimate goal of a safer and more effective treatment with moroctocog alfa.

References:
[1] Ahn JE, Karlsson MO, Dunne A, Ludden TM. 2008. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn 35(4):401-21
[2] Karlsson MO, Beal SL, Sheiner LB. 1995. Three new residual error models for population PK/PD analyses. J Pharmacokinet Biopharm 23:651–672

II-03: *Malidi Ahamadi* Population exposure –response analysis of "On-Off" time in Individuals with Parkinson Disease following Preladenant Treatment

Malidi Ahamadi
Merck Research Laboratories, Merck & Co., Inc., Whitehouse Station, NJ, USA;

Objectives: Preladenant is an Adenosine type 2A (A2a) receptor antagonist that was in development for Parkinson Disease (PD). Population exposure-response analysis was applied to: quantify efficacy and safety relationships for preladenant in a Phase 2B trial including individuals with Parkinson disease and motor fluctuations on levodopa therapy; to assess interaction with concomitant anti-PD medications; to identify subpopulations demonstrating differential response; and to assist future Parkinson's disease clinical studies.

Methods: A total of 199 individuals with moderate to severe idiopathic Parkinson disease provided data for this analysis. Individuals on a stable anti-parkinsonian treatment regimen were treated with placebo or oral preladenant, 1, 2, 5 or 10 mg BID. A hierarchical, longitudinal PK-PD model related predicted preladenant concentration to the probability of a patient being in the "off" state at each half-hourly assessment over the three days preceding a clinical visit.

Results: A two-compartment population PK model with transit compartment absorption model described preladenant concentration. The effect of concomitant anti-PD medication was modeled based on prior historical data in combination with the reported frequency of a given patient's treatment regimen. An Emax model of the synergistic effect of preladenant described the reduction in "off" probability as a function of time and concomitant anti-PD drug effect. To explore implications of the models for development decisions, statistically realistic predictions of how Preladenant affects key "off" time endpoints were generated. The final model was used to predict efficacy responses for subjects under possible treatment and population scenarios.

Conclusions: This work identified an exposure-relationship between preladenant and "off" probability. Concomitant treatment frequency was identified as a key covariate predicting this endpoint. Simulations based on this model provided a quantitative framework in support of dosing and other development recommendations. More frequent levodopa users have less "off" time response. Future clinical needs to consider this important factor.

References:

[1] Hauser, R. A.; Cantillon, M.; Pourcher, E.; Micheli, F.; Mok, V.; Onofrj, M.; Huyck, S.; Wolski, K. (2011). "Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial". The Lancet Neurology 10 (3): 221–229.
[2] Inaki F. Trockmiz, PhD, Tarja H. Naukkarinen, MSc, Hanna M. Ruottinen, MD, Urpo K. Rinne, MD, Ariel Gordin, MD, and Mats 0. Karlsson, PhD, Population pharmacodynamic modeling of levodopa in patients with Parkinson's disease receiving entacapone, Clin Pharmacol Ther 1998;64:106-16-16

II-04: *Maurice Ahsman* Modelling and simulation of oral GnRH Antagonist TAK-385 and testosterone-lowering response in Prostate Cancer Patients to Optimize Trial Design and Dose Selection

Maurice Ahsman (1), Hélène M. Faessel (2), Nelleke Snelder (1), David MacLean (2) and Peter Vis (1)
(1) LAP&P Consultants BV, Archimedesweg 31, 2333 CM Leiden, the Netherlands, (2) Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Objectives: To develop a PK/PD model of testosterone (T) suppression with the non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist TAK-385, and use it in prospective confirmatory trial simulations to select a dose resulting in >90% of pts with T ≤ 50 ng/dL (medical castration) for 48 wks.

Methods: PK and T data were obtained from data from 3 phase I/II clinical trials. In total, 104 healthy males and 174 prostate cancer patients contributed 2465 PK and 3445 T observations, after treatment with various TAK-385 maintenance doses (40-160 mg daily) for up to max 48 weeks. A PK/PD model was developed using non-linear mixed-effects modelling in NONMEM V7.2.0 [1]. Simulations were done to construct the exposure-effect curve, and predict the fraction of subjects with sustained T ≤ 50 ng/dL over a 48-week treatment period (80-120 mg OD, after a loading dose on day 1).

Results: A three-compartment model with first-order delayed absorption and first-order elimination and an exponential error model adequately described TAK-385 PK. T levels were described using a semi-mechanistic PK/PD model, which combined indirect response-based modelling of production and degradation processes (GnRH, testosterone) with competitive and reversible inhibition of endogenous GnRH binding by TAK-385, and down-regulation mechanisms of GnRH receptors. Age was included as a covariate for the endogenous agonist (GnRH) concentration at baseline to account for different baseline T between healthy men and prostate cancer patients. Simulations showed that the proportion of patients with sustained medical castration reached a maximum at doses of 100 mg OD and above, with minimal added benefit beyond 120 mg OD. Higher doses were associated with a more robust T lowering response vs lower dose regimens, taking the 95% CI of expected responders into account. Large variability in PK and PD responses required a sufficiently high maintenance dose to ensure that >90% pts achieve and maintain T ≤ 50 ng/dL.

Conclusion: This analysis provided an integrated understanding of the relationships between TAK-385 dose, exposure and efficacy to inform trial design and decision-making in oncology drug development. A clinical trial of 610 patients receiving TAK-385 120 mg OD, which can produce a larger and consistent treatment effect, has a prospective power of >90%, even when allowing for a 15% dropout.

References:

[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA

II-05: *Sihem Ait-Oudhia* A plateform PK/PD Model for Antibody Drug Conjugates Induced Myelosuppression

Ait-Oudhia Sihem
Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA and Department of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY

Objectives: To develop a unified model describing the pharmacokinetics (PK) of trastuzumab emtansine (TDM1) and brenduximab vedutin (SGN35), and their myelosuppressive effects in mice.

Methods: TDM1 and SGN35 PK and their effects on platelets (PLT) and neutrophils (ANC) counts were assessed in balbc normal or human xenografted mice after single or repeated doses and compared to control groups. Total trastuzumab concentrations were measured while total plasma concentrations for SGN35, the payloads (DM1 and MMAE for TDM1 and SGN35), and the antibodies (trastuzumab and anti-CD30 for TDM1 and SGN35) were extracted from the literature [1, 2]. MONOLIX and Berkeley Madonna were used to model the data.

Results: Two-compartment models with linear elimination and de-conjugation from the ADCs (kdec) described the PK of the 2 ADCs, and their respective payloads and monoclonal antibodies. Myelosuppression from both ADCs was captured with a series of five transit compartments representing cell proliferation and maturation in the bone marrow, and PLT or ANC in blood. A negative feedback loop accounted for the observed tolerance. TDM1 and SGN35 half-lives were estimated at 4.8 and 4.6 days and kdec were 0.46 and 0.12 h-1. The lifespans for PLT under TDM1 and ANC under SGN35 were 3.73 and 4.72 days. Comparison of alternative model performance suggested that TDM1 and SGN35 myelosuppressions are caused by different mechanisms: ADC binding to FcgR for TDM1 and payload-driven toxicity for SGN35 due to high lipophilicity of MMAE. Model based-simulations suggested that a 6-fold increase and 70% decrease in kdec of TDM1 and SGN35 would improve myelosuppression.

Conclusions: The proposed model successfully captured the PK and myelosuppressive effects of TDM1 and SGN35 and may serve as a general PK/PD platform for ADCs.

References:
[1] Erickson, H.K., et al. Mol Cancer Ther, 2012. **11**(5): p. 1133-42.
[2] Hamblett, K.J., et al. Clin Cancer Res, 2004. **10**(20): p. 7063-70.

II-06: *Ali Mohamed Ali* Population pharmacokinetics of the amodiaquine: pooling data across different studies to optimize dosing in neglected populations

Ali Mohamed Ali (1,2,3), Melissa Penny (1,2), Lesley Workman (4,5), Karen I. Barnes (4,5), Paolo Denti (4) on behalf of the WWARN Amodiaquine PKPD study group (5)
(1) University of Basel, Basel, Switzerland. (2) Swiss Tropical and Public Health Institute, Basel, Switzerland. (3) Ifakara Health Institute, Bagamoyo, Tanzania. (4) University of Cape Town, Cape Town, South Africa, (5) Worldwide Antimalarial Resistance Network

Objectives: To characterise the pharmacokinetics of the antimalarial amodiaquine (AQ) and its active metabolite desethylamodiaquine (DEAQ) to a) test whether higher cure rates with the fixed dose combination relate to higher drug exposure and b) inform optimal dosing if exposure is lower in neglected populations (e.g. very young children, pregnant women).

Methods: Pooled analysis of individual patient data from seven clinical trials [1-7] on AQ given as loose or fixed-dose formulation daily for 3 days either alone or in combination with artesunate (AS). Studies were conducted in six countries including both African and Asian populations. The dosage, drug formulation and sampling schedule varied between studies. Concentration-time data were analyzed using NONMEM 7.3 and FOCE-I. The model was developed starting with the most intensely sampled dataset and further data sets added step-by-step, as previously described [8]. Allometric scaling and maturation were used to adjust for differences in body size and age [9]. The effect of disease on PK was tested using an exponential function.

Results: A combined parent (AQ) and metabolite (DEAQ) model was used, with absorption through six transit compartments and a two-compartment disposition for AQ and three-compartment disposition for DEAQ. Patients receiving AS + AQ, either in loose or fixed-dose combination formulations, had higher bioavailability than those receiving AQ alone. Maturation of clearance (based on post-menstrual age) was found to improve the fit. Mature clearance for a 49 kg patient was estimated at 2710 L/h for AQ and 29.4 L/h for DEAQ. Clearance was lower in Thai pregnant women and higher in the patients from the Democratic Republic of Congo. A disease effect was found, with clearance doubling between the initiation of treatment and Day 3 when most symptoms had resolved.

Conclusions: The higher bioavailability of AQ given with AS in a fixed dose combination is consistent with previous reports [10] of higher efficacy of this fixed dose formulation. This study is the first to describe the maturation effect on clearance of AQ and DEAQ. The model can be used to optimize dosing regimens so that infants and younger children receive the same exposure levels as adults. The disease effect found in this study should be better characterized by including studies involving both healthy volunteers and malaria patients.

References:

[1] Adjei, G. O. et al. Effect of concomitant artesunate administration and cytochrome P4502C8 polymorphisms on the pharmacokinetics of amodiaquine in Ghanaian children with uncomplicated malaria. Antimicrob. Agents Chemother. 52, 4400–6 (2008)
[2] Mwesigwa, J. et al. Pharmacokinetics of artemether-lumefantrine and artesunate-amodiaquine in children in Kampala, Uganda. Antimicrob. Agents Chemother. 54, 52–9 (2010)
[3] Jullien, V. et al. Population pharmacokinetics and pharmacodynamic considerations of amodiaquine and desethylamodiaquine in Kenyan adults with uncomplicated malaria receiving artesunate-amodiaquine combination therapy. Antimicrob. Agents Chemother. 54, 2611–2617 (2010)

[4] Tarning, J. et al. Population pharmacokinetic and pharmacodynamic modeling of amodiaquine and desethylamodiaquine in women with Plasmodium vivax malaria during and after pregnancy. Antimicrob. Agents Chemother. 56, 5764–73 (2012)
[5] Rijken, M. J. et al. Pharmacokinetics of amodiaquine and desethylamodiaquine in pregnant and postpartum women with Plasmodium vivax malaria. Antimicrob. Agents Chemother. 55, 4338–42 (2011)
[6] Sinoul, V. et al. Pharmacokinetics and pharmacodynamics of a new ACT formulation : ArtesunatelAmodiaquine (TRIMALAC ~ following oral administration in African malaria patients. 34, 133–142 (2009)
[7] Stepniewska, K. et al. Population pharmacokinetics of artesunate and amodiaquine in African children. Malar. J. 8, 200 (2009)
[8] Svensson, E. et al. Integration of data from multiple sources for simultaneous modelling analysis: Experience from nevirapine population pharmac okinetics. Br. J. Clin. Pharmacol. 74, 465–476 (2012)
[9] Anderson, B. & Holford, N. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu. Rev. Pharmacol. Toxicol. 48, 303–332 (2008)
[10] WorldWide Antimalarial Resistance Network (WWARN) AS-AQ Study Group et al. The effect of dosing strategies on the therapeutic efficacy of artesunate-amodiaquine for uncomplicated malaria: a meta-analysis of individual patient data. BMC Med. 13, 66 (2015)

II-07: *Hesham Al-Sallami* Redefining normal variability of drug disposition

Hesham S Al-Sallami
School of Pharmacy, University of Otago, Dunedin, New Zealand

Objectives: The pharmacokinetics of many drugs are said to be predictable. This is often used to imply the ease of dosing or dose-adjustments. However, predictability requires both accuracy (lack of bias) and precision (reproducibility). In the context of pharmacokinetics, precision refers to the ability to achieve a specified target concentration in different individuals. Precision is the inverse of the variance between-subjects. In this setting the greater the between subject variability (BSV) in the parameters of a PK model the less precise/predictable the concentration will be across the population. BSV in PK parameters is quantified by the coefficient of variation (CV%). The current convention is that BSV in PK parameters is considered "low" (CV% ≤ 10%), "moderate" (CV% ~ 25%), or "high" (CV% > 40%).[1] The objective of this work is to explore the range of BSV values in population PK parameters.

Methods: A literature review of population PK studies from various data sources was conducted. Drug classes studied included psychotropics, immunosuppressants, cardiovascular drugs, and antibiotics. Estimates of clearance (CL) and volume of distribution (V) and their corresponding CV% were recorded.

Results: A total of 181 studies involving 95 drugs were reviewed. The mean CV% in CL/F was 40.3% and in V/F was 51.3%. The mean CV% in CL/F in predominately renally cleared drugs was 31% (after accounting for renal function) and those predominately hepatically cleared was 47.4%. Age, sex, weight, and renal function were among the most significant covariates reported across the drug classes.

Conclusions: According to the current convention most drugs show "moderate" to "high" BSV. The current convention needs to be recalibrated to consider that a low BSV in CL is < 25%, 25 – 50% is normal, and > 50% is high. Clinically, this means that a normal level of variability in CL would result in a 5- to 6-fold variability in steady state average plasma concentrations (the 95% interval of steady state average concentrations) and therefore for all drugs with a low therapeutic index, monitoring plasma concentration or response and dose-individualisation will be essential.

References:
[1] Rowland M, Tozer TN. Variability. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 333-55.

II-08: *Silvana Alvariza* Autoinduction of phenytoin hepatobiliary secretion as a mechanism for its nonlinear pharmacokinetics

Alvariza S, Ibarra M, Vázquez M, Fagiolino P.
Department of Pharmaceutical Sciences, Faculty of Chemistry Universidad de la República, Uruguay

Objectives: In order to understand the nonlinear pharmacokinetic behavior of phenytoin (PHT), a population pharmacokinetic model of PHT and its main metabolite, p-hydroxy-phenytoin (HPPH), including drug enterohepatic cycling was developed and compared with the classic saturable elimination model.

Methods: Eight healthy volunteers (6 men and 2 women) received orally 600 mg of PHT every 72 hours during a 10-day period (four dosing events at day 1, 4, 7 and 10). An immediate release tablet containing 100 mg of PHT was used (Comitoina, Roemmers Laboratories). In order to prevent loss of bioavailability due to PHT limited solubility in gastrointestinal fluids, each dose of 600 mg was divided in three administrations of 200 mg every 2 hours. Plasma levels of PHT and HPPH were measured at day 1 (12 and 24 hours post-dose) and at day 10 (20 samples obtained between 0 and 96 hours post-administration). Pharmacokinetic analysis was performed using NONMEM® 7.3 [1]. Structural and statistical models were evaluated with goodness of fit plots, Akaike information criterion and visual predictive checks.

Results: The final model included one compartment distribution for both PHT and HPPH, with first-order elimination. Fraction of HPPH produced by PHT elimination was fixed to 1, estimating the apparent volume of distribution (Vd) for both compounds. PHT enterohepatic cycling was included in order to account for observed multiple-peaks in plasma using a previously published model [2]. Increase in PHT and HPPH biotransformation clearance, and PHT secretion into bile (CLG) from day 1 to day 10 was included, in accordance to observations and reported PHT inductive properties [3]. This model showed a superior description of data than the classical PHT saturable elimination. Typical estimated parameters for a bodyweight of 70 kg were: PHT initial CL/F (1.35 L/h), PHT final CL/F (2.21 L/h), PHT Vd (61.8 L), PHT absorption constant rate (0.388 h-1), PHT final CLG/F (0.737 L/h), HPPH final CL/F (101 L/h), HPPH Vd (2450 L), constant rate for PHT enzyme and transporter induction (0.0208 h-1) and PHT reabsorption constant rate (0.156 h-1).

Conclusions: A model including PHT recirculation best-described observed PHT and HPPH data. In other dosage regimens, autoinduction of PHT recirculation could explain the decrease in systemic elimination and therefore its nonlinear accumulation.

References:

[1] Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J. NONMEM User's Guides 1989-2009; Icon Development Solutions, Ellicott City, MD, USA, 2009
[2] Ibarra, M., Vazquez, M., Fagiolino, P. Population pharmacokinetic model to analyze nevirapine multiple peaks profile after a single oral dose. JPKPD 2014; 41(4).
[3] Alvariza, S., Fagiolino, P., Vazquez, M., Feria-Romero, I., Orozco-Suarez, S. Chronic administration of phenytoin induces efflux transporters overexpression in rats. Pharmacological Reports 2014; 66.

II-09: *Claire Ambery* Balancing efficacy and risk: A case study of Phase 2 dose selection for an anti-inflammatory drug

C. Ambery(1), M. Beerahee(1)
(1) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, United Kingdom

Introduction: A novel IV anti-inflammatory drug is in development for the treatment of infectious disease. Clinical proof-of-pharmacology was demonstrated in healthy subjects by biomarker inhibition as well as for predecessor compound where 50-70% inhibition of biomarker was associated with 75% inhibition of inflammatory marker. A biomarker PK/PD relationship has previously been described by two-step sequential modelling. This is a Phase 2 dose selection case study for a new Captisol (sulfobutylether-beta-cyclodextrin, a solubilising agent) IV formulation. Captisol is well tolerated in healthy subjects, however clearance is delayed in renal impairment [3], a clinical concern given disease. Drug exposure limitation based on toxicology findings was also imposed for the novel drug.

Objectives: Phase 2 dose selection based on 1) Captisol exposure limitations, 2) drug exposure limitations, and 3) biomarker-response relationship.

Methods: Captisol: Captisol literature review performed [1,5]. Captisol PK model of [4] used to create Berkeley Madonna (BM) simulation model. BM model used to simulate new drug scenarios. To enable simulation across spectrum of renal function the relationship between Captisol plasma clearance and creatinine clearance was defined by use of digitised data from Fig.4(B) of [3] and Fig.2 of [4] excluding renal dysfunction subjects during hemodialysis data. A linear model was fitted to the digitised data. Safety: Simulations to predict the proportion of subjects exceeding the exposure limit based on toxicological findings were performed. One thousand NONMEM trial simulations of 100 subjects per dose level were performed for each dose scenario. Biomarker: The predicted exposures from the safety simulation were used to perform sequential biomarker simulations. One thousand NONMEM trial simulations of 100 subjects per dose level were performed for each dose scenario. The level of biomarker inhibition at Ctrough and Cavg was evaluated.

Results: Captisol simulated over creatinine clearance range 10 to 120 mL/min [2]. For formulation ratio of Captisol to novel drug, levels within previous clinical experience, mitigating clinical concern. Top dose selected based on minimising proportion of subjects exceeding safety limit. Figure 1 shows predicted biomarker inhibition for Cavg dose scenarios.

Conclusions: Simulation of biomarker exposure-response relationship, together with Captisol and drug concentration facilitated selection of Phase 2 dose.

References:

[1] Abel S, Allan R, Gandelman K, Tomaszewski K, Webb DJ, Wood ND. Pharamcokinetics, safety and tolerance of voriconazole in renally impaired subjects. *Clin Drug Res*. 2008;28(7):409-420.
[2] Guidance for Industry: pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labelling. Rockville (MD): US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and research, 1998 May.
[3] Luke DR, Tomaszewski K, Damle B, Schlamn HT. Review of basic and clinical pharmacology of sulfobutylether-β-cyclodextrin (SBECD). *J Pharma Sci.* 2010;99(8):3291-3301.

[4] Luke DR, Wood ND, Tomaszewski K, Damle B. Pharmacokinetics of sulfobutylether-β-cyclodextrin (SBECD) in subjects on hemodialysis. *Nephrol Dial Transplant*. 2012;27:1207-1212.
[5] Turner RB, Martello JL, Malhotra A. Worsening renal function in patients with baseline renal impairment treated with intravenous voriconazole: A systematic review*. Int J Antimicrob Agents.* 2015;46(4):362-366.

II-10: *Yasunori Aoki* Model Averaging and Selection methods for model structure and parameter uncertainty quantification

Yasunori Aoki and Andrew C. Hooker
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: There have been several attempts through model averaging and model selection to weaken the assumptions around model structure by pre-specifying multiple possible model candidates prior to the analysis and automatically averaging or selecting the model structures [1]. However, to the best of authors' knowledge, a methodology to combine the model structure and parameter estimation uncertainties to quantify the overall modelling uncertainty is not available. In this poster we extend our work in [2] and introduce a few possible model averaging/selection methodologies and compare the accuracy of these methods in the prediction of the minimum effective dose using a simulated dataset of FEV1 mimicking Phase IIb clinical trial used in [2].

Methods:
Step1: Create bootstrap datasets.
Step2: Estimate parameters for each model for each bootstrap dataset.
Step3: Simulate dose-endpoint relationships using each set of parameters estimated.
Step4: Construct probability of success vs. dose relationship using one of the following model schemes.
1): model selection using Akaike Information Criterion (AIC) based on OFV from the original dataset.
2): model selection using AIC based on the OFVs from the bootstrap datasets.
3): model averaging weighted by AIC based on the OFV from the original dataset.
4): model averaging weighted by AIC based on the OFVs from the bootstrap datasets.
In addition, we have conducted a numerical identifiability test using preconditioning [3,4] to weight out the models that are not locally practically identifiable.
Step5: Choose one of the candidate doses based on the probability of success vs. dose relationship.

Results: The proposed methods are made available in an open-source GUI based software at www.bluetree.me (also available as an r-script).
We have observed that model selection (schemes 1, 2) have done consistently better than model averaging (schemes 3, 4) when predicting the minimum effective dose. In addition, the confidence level for the correctly chosen minimum effective dose for scheme 2 was marginally but consistently higher than scheme 1. The identifiability test did not influence the results of the model selection; however, did marginally improve the results of model averaging.

Conclusion: Based on our numerical experiment we recommend model selection scheme 2. This method can be used as a way to pre-specify the possible model structures before obtaining the data so as to increase the objectivity of the model based analysis using nonlinear mixed effect models.

References:
[1] Frank Bretz, José C. Pinheiro, and Michael Branson. "Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies." Biometrics 61.3 (2005): 738-748.
[2] Yasunori Aoki, Bengt Hamrén, Daniel Röshammar, and Andrew C. Hooker, "Averaged Model Based Decision Making for Dose Selection Studies", PAGE 23 (2014) Abstr 3121 [www.page-meeting.org/?abstract=3121]
[3] Yasunori Aoki, Rikard Nordgren, and Andrew C. Hooker, "Preconditioning of Nonlinear Mixed

Effect models for Stabilization of the Covariance Matrix Computation", PAGE 24 (2015) Abstr 3586 [www.page-meeting.org/?abstract=3586]
[4] Yasunori Aoki, Rikard Nordgren, and Andrew C. Hooker. "Preconditioning of Nonlinear Mixed Effects Models for Stabilisation of Variance-Covariance Matrix Computations." The AAPS journal (2016): 1-14.

II-11: *Manel Aouri* Population pharmacokinetics analysis of dolutegravir in HIV-1 infected individuals

Manel Aouri(1), Monia Guidi (1,2), Matthias Cavassini(3), Thierry Buclin(1), Laurent A. Decosterd(4), Chantal Csajka (2,3), and the Swiss HIV Cohort Study.

1 Division of Clinical Pharmacology, University Hospital Center, University of Lausanne, Lausanne, Switzerland, 2 School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland , 3Division of Infectious Diseases, University Hospital Center, University of Lausanne, 4Innovation & Development, Laboratory of Clinical Pharmacology, Service of Biomedicine, University Hospital and University of Lausanne, Lausanne, Switzerland

Objectives: Dolutegravir (DTG), the latest integrase inhibitor (INIs) approved for HIV treatment is coformulated in a single tablet regimen with abacavir and lamivudine. DTG has demonstrated potent antiviral activity and a very good tolerability and is widely prescribed in HIV-infected patients (1). DTG is primarily metabolized via UDP-glucuronosyltransferase (UGT 1A1) with a minor component of CYP3A4 (2). The aim of this observational study was to characterize DTG pharmacokinetic profile, to quantify interpatient variability and to identify potential factors that could influence drug exposure.

Methods: All dolutegravir plasma concentrations data were collected as part of routine therapeutic drug monitoring performed in our centre, between June 2014 and December 2015 from HIV treatment-naive and experimented patients. A population PK analysis was performed by comparing various structural models using NONMEM®. The effect of relevant demographic factors and co-medications on dolutegravir disposition was explored.

Results: A total of 594 plasma levels were measured in 514 HIV-positive patients under steady state regimen conditions. Plasma concentrations ranged between 31 and 7971 ng/mL. A one-compartment model with first order absorption and elimination best characterized dolutegravir pharmacokinetics. Average DTG clearance was 0.93 (L/h), volume of distribution 18.9 (L), and absorption rate constant 1.27 (h^{-1}).The inter-subject variability on CL was estimated at 27%. Among the demographic covariates tested, body weight and age influenced positively and moderately DTG CL (29% and 24% respectively) as well as smoking status (17%). Coadminisation of atazanavir decreased DTG clearance by 38% and the association of darunavir increased the clearance of DTG (14%).

Conclusions: The variability in DTG pharmacokinetics appears lower than for other antiretroviral drugs. Several covariates were identified impacting DTG exposure however their effect appears to be relatively modest and seems not to be clinically significant except for tazanavir coadministration.

References:

[1] FDA. 2013. TIVICAY (dolutegravir) FULL PRESCRIBING INFORMATION. administration FaD, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf.

[2] Castellino S, Moss L, Wagner D, Borland J, Song I, Chen S, Lou Y, Min SS, Goljer I, Culp A, Piscitelli SC, Savina PM. 2013. Metabolism, excretion, and mass balance of the HIV-1 integrase inhibitor dolutegravir in humans. Antimicrob Agents Chemother 57:3536-3546.

II-12: *Hyun-moon Back* Development of QT prolongation model in guinea pig with hERG assay-in vivo PK- in-vivo QT effect to guide decision making in early drug discovery

Hyun-moon Back (1), Byungjeong Song (1), Sudeep Pradhan (1), Younghoon You (1), Eben Jung (1), Jung-woo Chae (2), Hwi-yeol Yun* (1), Kwang-il Kwon* (1)
(1) College of Pharmacy, Chungnam National University, Korea, (2) Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore

Objectives: hERG assay is a one of traditional approaches for evaluating cardiac safety of drug in early drug discovery [1]. But this assay has major limitation that it does not consider PK properties of drug candidates leading to a weak correlation between in vitro (hERG IC_{50}) and in vivo (delta QTcB) tests. For accurate prediction of QT prolongation in early drug development process, more improved evaluation method is required. In this study, we built the model for predicting QT prolongation considering hERG assay and PK parameters as well as in-vivo QT prolongation in guinea pig.

Methods: For making prediction model of QT prolongation, 14-drugs were selected from each of the four groups that were classified high-, moderate-, minor- and no-risk based on hERG assay. PK profiles and QTcB effect of each drug were obtained after IV administration in guinea pig [2]. PK parameters were estimated by non-compartmental analysis using Phoenix WinNonlin 6.4 and QT interval of each drug was corrected by QTcB equations. Using obtained results, QT prediction model was developed both with multivariate analysis and linear mixed effect model using R and NONMEM.

Results: Using multivariate analysis, two equations were developed:

1. % changes of QTc interval = -3.72*IC50 + 0.0015*IC50*(AUC_{all}) -0.0053*(AUC_{all}) +29.41
2. % changes of QTc interval = -2.31*IC50 – 0.0014*(Cmax) + 28.40

AUC showed better correlation with delta QTcB and hERG IC_{50} than Cmax in multivariate analysis (R^2: 0.46>0.39). Additionally, linear mixed effect model was developed in NONMEM and the final model, delta QTc interval can be estimated from AUC, Cmax and hERG IC50 value. Exponential model for explaining inter-individual variability was used only on AUC (95.8%) and constant coefficient of variance model was used as a residual error model (43.4 %).

Conclusions: Model for predicting delta QT interval considering hERG IC50 value and PK parameters of each drugs was successfully developed. Equations from multivariate analysis were simple but cannot considering variability. The final linear mixed effect model, in vivo QT prolongation can be estimated more accurately considering both hERG IC50 results and PK parameters (AUC, C_{max}) of a given drug.

References:
[1] U.S. Department of Health and Human Services Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for Industry, S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.
[2] Testai L, Calderone V, Salvadori A, Breschi MC, Nieri P, Martinotti E. QT prolongation in Anaesthetized Guinea-pigs: An Experimental Approach for preliminary screening of torsadogenicity of drugs and drug candidates. J Appl Toxicol (2004) 24:217-222.

II-13: *Suruchi Bakshi* Explaining the unexpected multi-stationarity in a nonlinear model of prolactin response to dopamine D2 receptor antagonists

Suruchi Bakshi (1), Elizabeth C. de Lange (1), Piet H. van der Graaf (1), Meindert Danhof (1), and Lambertus A. Peletier (2)
(1)Systems Pharmacology, Division of Pharmacology, LACDR, Leiden University, (2) Mathematical Institute, Leiden University

Objectives: To explain the unexpected multi-stationarity observed in a nonlinear precursor-pool model of prolactin (PRL) response to dopamine D_2 receptor antagonists, to extract meaningful parameter regions and to gain insight into the model behaviour using the techniques of dynamical systems analysis.

Methods: The nonlinear PRL pool model was converted into a dimensionless version using suitable concentration and time scaling. Steady states (SSs) of the dimensionless model were determined and their stability was studied using phase-plane analysis. Bifurcation analysis was performed to study the change of stability properties with changes in a critical parameter. Phase-plane analysis, combined with simulations, was used to explain the dynamics of the model in response to a drug challenge and the observed multi-stationarity.

Results: The pharmacodynamics of PRL in plasma has been modelled by means of a precursor-pool model which includes a positive feedback loop of plasma PRL on its own synthesis in the lactotroph pool, making it a nonlinear system [1]. Using mathematical analysis we have shown that positive feedback has resulted in occurrence of multiple SSs with different stability properties. One of the SSs is the baseline PRL in absence of drug administration. This is the physiologically desired SS, whereas the other SS is physiologically undesired. Stability of each SS, coupled with the drug PK, plays a role in determining which SS is predicted by the model. We have been able to deduce a parametric restriction under which the desired SS is stable. The work highlights the importance of mathematical analysis in pharmacological models [2].

Conclusions: Techniques of dynamical systems analysis of differential equation have been successfully applied to the nonlinear model of PRL response to explain the observed multi-stationarity and the parametric dependence of stability properties.

References:
[1] Stevens J, Ploeger B, Hammarlund-Udenaes M, Osswald G, van der Graaf PH, Danhof M and de Lange ECM, Mechanism-based PKPD model for the prolactin biological system response following an acute dopamine inhibition challenge: quantitative extrapolation to humans. Journal of Pharmacokinetics and Pharmacodynamics. 2012;39(5):463-477.
[2] Bakshi S, de Lange ECM, vd Graaf Piet H, Danhof M and Peletier LA, Understanding the behaviour of systems pharmacology models: mathematical analysis of differential equations. CPT: Pharmacometrics and Systems Pharmacology, Submitted.

II-14: *Violeta Balbás Martínez* Target evaluation for Inflammatory Bowel Disease (IBD) using a Systems Pharmacology model

Violeta Balbás-Martínez(1)-Leire Ruiz-Cerdá(1), Ignacio González-García(4), Itziar Irurzun-Arana(1), José David Gómez-Mantilla(1-2), Chuanpu Hu(4), Honghui Zhou(4), An Vermeulen(5), Iñaki F. Trocóniz(1-2).
(1)Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, University of Navarra, Pamplona, Spain. (2)IdiSNA, Navarra Institute for Health Research. Navarra, Spain (3)Pharma Mar, Madrid, Spain (4)Model Based Drug Development, Janssen Research and Development, LLC, Spring House, PA 19477, USA (5)Janssen Research and Development, a division of Janssen Pharmaceutica NV, Beerse B-2340, Belgium

Objectives: To develop a Systems Pharmacology (SP) model for IBD able to evaluate therapeutic targets for different types of IBD patients, focused on the change in the Crohn Disease Activity Index (CDAI) in each scenario. Additionally it was intended to identify a subgroup of patients non responders to an anti-TNFα therapy (current standard) and propose alternative therapies for such individuals.

Methods: A Boolean Network model, based on an exhaustive bibliographic review, was implemented in the SP platform AITOR [1]. The network contained 48 nodes (20 of them reported to be altered in IBD patients) and 226 interactions. Simulations of the immune response were performed assuming chronic response to four different types of microbial antigens. CDAI was analysed through the increase or decrease of the relative expression of the main nodes associated with clinical manifestations in IBD (Metalloproteinases, Perforin and Granzime B) [2-3]. Relative expression of nodes was calculated as obtaining the activation probability of each node after the network reached the attractor state. The network was evaluated comparing the results of the simulations to the reported results of clinical trials for five investigated molecules: anti-IFNγ, anti-TNFα, anti-IL2, anti-IL17 and anti-IL21.

Results: Only anti-TNFα decreased the simulated CDAI score in typical IBD patients. Anti-IL17 showed a slight improvement in the simulated CDAI score. Anti-IFNγ, anti-IL2 and anti-IL21 did not show any improvement of the CDAI score when simulated alone. Simulations of an anti-TNFα therapy showed less efficacy in patients with antigen impairment elimination (alteration in NK or Defensins function). A combined simulated therapy of anti-IL17, anti-TNFα and anti-IFNγ showed an improvement in the CDAI score reduction compared to anti-TNFα alone.

Conclusions: The obtained results satisfactory replicated the outcome of reported clinical trials. Anti-TNFα may not show efficacy in individuals with impaired antigen elimination. A combination of anti-IL17, anti-TNFα and anti-IFNγ could show more improvement in the CDAI score than other therapies. The proposed SP model is potentially useful to identify new therapeutic targets and to optimize therapy combinations. Simulation of more polymorphisms could lead to efficient patient stratification.

References:

[1] Itziar Irurzun-Arana, Methodology for Boolean Modeling of Biological Networks Applied to Systems Pharmacology. PAGE meeting 2015 conference abstract http://bit.ly/1GOyLRx.
[2]Biancheri, Paolo, Antonio Di Sabatino, Gino R. Corazza, and Thomas T. MacDonald. 2013. “Proteases and the Gut Barrier.” Cell and Tissue Research 351 (2): 269–80.
[3] Cupi, Maria Laura, Massimiliano Sarra, Irene Marafini, Ivan Monteleone, Eleonora Franzè, Angela Ortenzi, Alfredo Colantoni, et al. 2014. “Plasma Cells in the Mucosa of Patients with Inflammatory Bowel Disease Produce Granzyme B and Possess Cytotoxic Activities.” Journal of Immunology 192 (12): 6083–91.

II-15: *Kathryn Ball* Prediction of food effect in the Chinese population using a PBPK model developed in a Caucasian population

Kathryn Ball (1), Maud Beneton (1), Emilie Leroux (1), Marylore Chenel (1)
(1) Clinical Pharmacokinetics and Pharmacometrics Department, Institut de Recherches Internationales Servier, Suresnes, France, (2) Nonclinical Pharmacokinetics and Biopharmaceutical Research Department, Technologie Servier, Orleans, France

Objectives: A PBPK model for an orally administered Servier compound (S1) was built in order to predict its PK in Chinese patients, both in the presence and absence of food, to aid the design of the first in man study in the Chinese population. The predictions were then compared to the observed data from the clinical study.

Methods: A PBPK model was built for S1 in the Simcyp software, using *in vitro* data including solubility at a range of pH values, Caco-2 permeability, plasma protein binding, and intrinsic clearance in hepatocytes. The model was first qualified using *in vivo* plasma concentration-time data from a dose-finding study in Caucasians. A Chinese population exists within Simcyp, which takes into account differences in demographic characteristics and enzyme abundance [1]. The model was then used to simulate the therapeutic dose in Chinese patients, and compared with the data from European Caucasian patients. The model was then used to simulate the PK in Chinese patients in the presence and absence of food, in order to anticipate a food effect [2]. The data from a subsequent clinical study in Chinese patients was used to evaluate the goodness of these predictions.

Results: The predicted geometric mean AUC_{ss} of S1 in Chinese patients (fasted) was 1.5-fold of that in European Caucasian patients (fasted), compared to the observed Chinese-to-European AUC_{ss} ratio of 1.4-fold. The food effect simulation in the Chinese population using the PBPK model predicted an S1 AUC_{ss} in the fed state which was 1.0-fold of the AUC_{ss} in the fasted state. This was confirmed by the observed data, which also gave a 1.0-fold AUC_{ss} ratio (fed vs fasted).

Conclusions: The AUC_{ss} of the Chinese patients was well predicted by the PBPK model. Demographic differences, such as the lower abundance of CYP3A4 in Chinese patients versus Caucasians, and the smaller liver size of Chinese versus Caucasians, result in a lower hepatic clearance in Chinese patients. Demographic differences which affect absorption, and which were not taken into account in the model, may affect the fraction absorbed of S1. Nevertheless, a negligible food effect was predicted in the Chinese population using the PBPK model, and this was found to be in very good agreement with the observed data, which also showed a negligible food effect.

References:
[1] Barter ZE, Tucker GT, Rowland-Yeo K. Differences in cytochrome P450-mediated pharmacokinetics between Chinese and Caucasian populations predicted by mechanistic physiologically based pharmacokinetic modelling. *Clin Pharmacokinet.* 2013. 52 : p. 1085-1100.
[2] Jamei M, Turner D, Yang J, Neuhoff S, et al. Population-based mechanistic prediction of oral drug absorption. *AAPS J,* 2009. 11 : p. 225-237.

II-16: *Catalina Barceló* Population pharmacokinetics analysis of elvitegravir and cobicistat in HIV-1 infected individuals

Catalina Barceló (1), Frédéric Gaspar (2), Manel Aouri (1), Alice Panchaud (2), Margalida Rotger (1), Monia Guidi (1,2), Matthias Cavassini (1), Thierry Buclin (1), Laurent A. Decosterd (1) and Chantal Csajka (1,2) and the Swiss HIV Cohort Study.
(1) University Hospital Centre of Lausanne, Switzerland, (2) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Switzerland.

Objectives: Co-formulated elvitegravir (EVG), cobicistat (COBI), tenofovir disoproxil fumarate and emtricitabine is among the preferred regimens for first-line antiretroviral therapy. This study aimed to develop a population pharmacokinetic model for EVG and COBI and identify individual factors and co-medications influencing their disposition, taking into consideration the interaction between both compounds.

Methods: Study population included 144 HIV-infected individuals who provided 186 and 167 EVG and COBI plasma concentrations respectively. First, distinct analyses were conducted for both drugs, including individual demographic, clinical and genetic factors as potential covariates (NONMEM®). Secondly, EVG and COBI interaction was evaluated through diverse inhibitory models. Simulations based on the final model were used to compare expected drug concentrations under standard and alternative dosage regimens.

Results: Clearance with between-subject variability (BSV %CV) was 7.6 L/h (16.6% CV) and volume of distribution 61 L for EVG, and respectively 15.8 L/h (43.6% CV) and 87.3 L for COBI. Concomitant administration of non-boosted atazanavir decreased EVG clearance (CL/F_{EVG}) by 35%, likely due to UGT1A1 inhibition. Concomitant administration of non-boosted atazanavir and ritonavir-boosted darunavir decreased COBI clearance by 49%, and 28%, respectively. The final interaction model included COBI exposure ($AUC_{0\text{-}24}$) on CL/F_{EVG}. A 2 fold increase in AUC_{COBI} induced a 46% reduction of CL/F_{EVG} and AUC_{COBI} decreased CL/F_{EVG} BSV by 51.3%. Simulations confirmed that EVG reduced dose of 85 mg co-administered with COBI and atazanavir produces a concentration time course comparable to the standard regimen without atazanavir.

Conclusions: EVG and COBI pharmacokinetic variability appears to be mainly explained by drug-drug interactions that may be encountered in routine clinical practice. These models might serve to derive percentile reference curves or implemented in a Bayesian tool for dosage adjustment.

II-17: *Charlotte Barker* Simultaneous modelling of antimicrobial pharmacokinetic data from birth to adolescence: using different penicillins to inform a common maturation function

Charlotte Barker (1,2), Karin Kipper (1,3), Georgina Thompson (1,4), Min Kim (1,5), Mark Turner (6), Atholl Johnston (7), Mike Sharland (1), Joe Standing (2,1)

(1) Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's University of London, London, UK (2) UCL Institute of Child Health, London, UK (3) Institute of Chemistry, University of Tartu, Tartu, Estonia (4) University of Exeter, Exeter, UK (5) UCL School of Pharmacy, London, UK (6) Department of Women's and Children's Health, University of Liverpool, Liverpool, UK (7) Clinical Pharmacology, Barts and The London School of Medicine and Dentistry, London, UK

Objectives: Developmental physiology and ontogeny are known to affect drug disposition in neonates and children. Thus improving our understanding of developmental pharmacology is an important component of paediatric dose optimization strategies. This analysis aimed to use interim data from NAPPA, a multicentre, multi-drug paediatric penicillin pharmacokinetic (PK) study [1], to inform a common maturation function (MF) from birth to adolescence for two drugs: benzylpenicillin and piperacillin.

Methods: Eligible participants were recruited at participating hospitals with informed consent. The antibiotic dosing regimen was as per standard care. Study blood samples (0.5mL each) were obtained with routine samples or at recommended times, then frozen and analysed in retrospect using high-performance liquid chromatography with tandem mass spectrometry. PK data from both penicillins were analysed simultaneously with a joint PK model implemented in non-linear mixed-effects modelling software (NONMEM v7.3, Icon plc), with a priori allometric weight scaling on both volume (Vd) and clearance (CL), and a shared postmenstrual age (PMA) driven MF on CL [2,3]. The importance sampling (IMP) estimation method was used to obtain the objective function value (OFV). The study had NRES Research Ethics Committee approval.

Results: For this analysis, interim NAPPA PK data were available for participants on benzylpenicillin (n=45) and piperacillin/tazobactam (n=29). The study population included 46 neonates (25 preterm), and 28 infants and children (up to 12 years-old). Using a joint one compartment population PK model, the combined data were analysed simultaneously and the optimization was completed with successful convergence. The OFV was 1589.374. The final parameter estimates were: 3.22 L/h/70 kg for benzylpenicillin CL and 10.9 L/70kg for Vd; 6.89 L/h/70 kg for piperacillin CL and 15.4 L/70kg for Vd, and for the common MF, the final parameter estimates were: 3.55 for the Hill coefficient and a PMA of 39.7 weeks for the maturation half-time (TM50).

Conclusions: Interim paediatric PK data from two penicillins were successfully analysed simultaneously using a joint model with a common MF. Allometric weight scaling with a sigmoidal MF was used as standardised parameterization to facilitate extrapolation and learning across drugs with similar PK [4]. Future work will include incorporating data from additional NAPPA study penicillins and retesting the model with the final dataset.

References:

[1] NAPPA: Neonatal and Paediatric Pharmacokinetics of Antimicrobials Study. EudraCT 2013-002366-40. https://clinicaltrials.gov/ct2/show/NCT01975493

[2] Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci 2013;

102: 2941-52.
[3] Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child 2013; 98: 737-44.
[4] Germovsek E, Barker CIS, Standing JF. An Argument for Standardised Scaling: Comparison of Methods for Scaling Clearance in Children. PAGE poster presentation (PAGE 24 (2015) Abstr 3635). Abstracts of the Annual Meeting of the Population Approach Group in Europe. ISSN 1871-6032. Available at: www.page-meeting.org/?abstract=3635

II-18: *Ana Bastos* Using modeling and simulation to design and evaluate dosing strategies for temocillin in haemodialysis patients

Miranda Bastos AC (1,2) , Vandecasteele SJ (3), Capron A (4), Tulkens PM (1), Spinewine A (2), Van Bambeke F (1)

(1) Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium (2) Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium (3) Department Nephrology and Infectious Diseases, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium (4) Department of Clinical Chemistry, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

Objectives: Temocillin is an anti-Gram-negative β-lactam active against many ESBL-producing Enterobacteriaceae, but with limited population pharmacokinetics data on end-stage renal disease patients undergoing haemodialysis. The purpose of this study was to develop a joint PK model of total and unbound temocillin serum concentrations in this patient population. In addition, this model was used to design and evaluate a dosing regimen aiming for a 90% probability of target attainment (unbound concentrations at least 40% of the dosing interval above the largest minimal inhibitory concentration (40%$fT > MIC$) of the main susceptible organisms ($\leq$ 16mg/L).

Methods: Patients were administered a dose of 1, 2, or 3g of temocillin (total of 61 doses) followed by an interdialytic period (off-dialysis) of 20, 44, or 68h, respectively, and dialysis period of 4h. A nonlinear mixed effects model was fitted, taking both total and unbound temocillin concentrations into account. The model was evaluated by bootstrap analysis and prediction-corrected visual predictive check. 2000-subject Monte Carlo simulation was conducted to determine the required dose to achieve 90% probability of target attainment over a wide range of patients' weights (50-120kg). These simulations also investigated the performance of various clinically feasible dosing regimens. Data analyses were performed using NONMEM 7.3, Pirana, PsN and R.

Results: A total of 429 serum samples was collected from 16 patients. An open two-compartment model with non-linear binding to albumin (Langmuir model) and mixed order elimination, best characterized the profiles of temocillin concentrations over time. Weight on clearance and volume of distribution parameters using allometric scaling improved the fit. The mean and between-patient variability for central volume of distribution were 22.7L/70kg (38.2%). Vmax for elimination was estimated to be 97.7mg/h/70kg, whilst the Km was 216mg/L. Temocillin clearance was found to decrease with dose increases. Model-based simulations suggested that 2g every 24 hours regardless patients's weight or the haemodialysis regimen (24, 48 or 72h interdialytic interval), maintain drug concentrations over a MIC of 16 mg/L for at least 40 % of the dosing interval.

Conclusions: A joint PK model describes the time course of temocillin in patients undergoing haemodialysis. Modeling and simulation of temocillin PK suggest that administration of standard doses are likely to result in underdosing. A new dosing regimen has been developed to more consistently achieve PKPD targets.

II-19: *Levy Batista* Mixed-effects ARX model identification of dynamical systems

Levy Batista(1,3), Thierry Bastogne(1,2,3), and El-Hadi Djermoune(1)
(1) CRAN CNRS UMR 7039, Nancy, France (2) INRIA BIGS, Vandoeuvre-lès-Nancy, France (3) CYBERnano, Villers-lès-Nancy, France

Objectives: With the advent of realtime biotechnologies, most of biological responses measured during in-vitro or in- vivo experiments exhibit non-linear behaviors and mixed effects models are often used to better characterize the responses. Parameter and confidence intervals estimation involve numerical integration, linearization or stochastic approximation algorithms [1]. Instead of modeling the response we propose a method in which each biological process is regarded as a dynamical system with input-ouput variables and cofactors. We show that this approach allows to use classical linear methods.

Methods: Firstly, we suppose that the response of each biological unit is the output of a linear time invariant system described by an autoregressive model structure with external input (ARX) [2]. The drug administration is considered as the input signal. To account for the variability within and between biological units, we introduce mixed effects in the ARX model. Data are assumed to be recorded at a constant sampling rate. The basic EM algorithm is implemented without approximation to estimate the model parameters under the likelihood function [3]. Moreover, Fisher information matrix is determined by using Louis method [4].

Results: We show how mixed-effects can be introduced in black-box modeling for the identification of a population of dynamic systems. We have determined parameter estimation and confidence intervals of an ARX model structure. We show relevance of the proposed solution in simulation and using real in-vitro data coming from realtime cell impedance measurements.

Conclusions: New biotechnologies allow to use system identification models where the response of individuals is seen as the output of a system with unknown parameters. The proposed method suggests that, in some cases, it is possible to use linear mixed-effects estimation methods to characterize non-linear responses.

References:
[1] M. Lavielle, Mixed Effects Models for the Population Approach. Models, Tasks, Methods & Tools. Chapman & Hall/CRC Biostatistics Series, 2014.
[2] L. Ljung, System Identification, Theory for the User. PreWiley-Hall, 1987.
[3] A. P. Dempster, N. M. Laird, and D. B. Rubin, “Maximum likelihood from incomplete data via the EM algorithm,” Journal of the royal statistical society, Serie B, vol. 39, no. 1, pp. 1–38, 1977.
[4] T. A. Louis, “Finding the observed information matrix when using the em algorithm,” Journal of the Royal Statistical Society. Series B (Methodological), vol. 44, no. 2, pp. pp. 226–233, 1982.

II-20: *Brendan Bender* An integrated pharmacokinetic-pharmacodynamic modeling analysis of T-DM1–induced thrombocytopenia and hepatotoxicity in patients with HER2-positive metastatic breast cancer

Bender B (1), Quartino A (2), Li C (2), Chen, S-C (2), Smitt M (2), Strasak A (2), Chernyukhin N (2), Wang B (2), Jin J (2), Girish S (2), Friberg LE (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden ; (2) Genentech Inc, San Francisco, CA

Objectives: T-DM1 is an antibody-drug conjugate for HER2-positive metastatic breast cancer and is associated with Grade 3/4 adverse events (AE) of thrombocytopenia (TCP) and hepatotoxicity [1]. A PKPD model was developed to describe platelet and ALT/AST transaminase response to T-DM1, and to compare weekly (q1w) regimens to the approved dose of 3.6 mg/kg every three weeks (q3w).

Methods: The PKPD model was fit to platelet, ALT, and AST data from five T-DM1 clinical trials (658 patients) using NONMEM software and the FOCE with INTERACTION algorithm. Doses ranged from 0.3–4.8 mg/kg q3w and 1.2–2.9 mg/kg q1w. The platelet model consisted of a proliferative "pool" compartment containing feedback, three transit delay compartments, and a circulation compartment modified from a previous analysis [2]. For ALT and AST, a similar model structure was used but with a zero order production rate for the pool compartment and no feedback. T-DM1 serum concentrations acted directly on the production rates of model pool compartments, describing the within-cycle oscillations of platelets and ALT/AST transaminases. An additional, slowly developing effect was described using a T-DM1 effect compartment. Patient baseline characteristics were tested as covariates on final model parameters. T-DM1 dose modification rules were incorporated into the model based on prescribing information. Model simulations compared dose exposure outcomes between q1w regimens which matched T-DM1 steady state exposure (1.2 mg/kg q1w) and steady state maximum concentrations (2.4 mg/kg q1w) to the approved dose. Posterior predictive checks (PPCs) with the model evaluated predictability for Grade ≥ 3 platelet, ALT, and AST using a Phase III internal evaluation dataset [3].

Results: PPCs showed that the model well-predicted the observed instances of Grade ≥ 3 TCP (18%), ALT (4.1%) and AST (6.5%). T-DM1 driven ALT and AST responses were highly correlated, but not with platelet response. Asian ethnicity was a covariate for Grade 3 TCP. The 2.4 mg/kg q1w regimen resulted in the highest dose intensity (2.07 mg/kg/wk) compared to the 1.2 mg/kg q1w regimen (1.15 mg/kg/wk) and the approved dose (1.18 mg/kg/wk).

Conclusions: Via simulations, q1w dose regimens are found to be associated with more dose modifications due to more frequent Grade 3 events predose. The simulated 2.4 mg/kg q1w dose provided the highest T-DM1 dose intensity. Asian patients are predicted to have higher instances of Grade 3/4 TCP.

References:
[1] Diéras V, Harbeck N, Budd GT, Greenson JK, Guardino AE, Samant M, Chernyukhin N, Smitt MC, Krop IE. Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis. J Clin Oncol. 2014 Sep 1;32(25):2750-7.
[2] Bender BC, Schaedeli-Stark F, Koch R, Joshi A, Chu YW, Rugo H, Krop IE, Girish S, Friberg LE, Gupta M. A population pharmacokinetic/pharmacodynamic model of thrombocytopenia characterizing the effect of trastuzumab emtansine (T-DM1) on platelet counts in patients with HER2-positive metastatic breast cancer. Cancer Chemother Pharmacol. 2012 Oct;70(4):591-601.

[3] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K; Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov 8;367(19):1783-91.

II-21: *Andrzej Bienczak* Semi-physiological pharmacokinetic/pharmacogenetic model with circadian rhythm for the characterisation of nevirapine pharmacokinetics in African children.

Andrzej Bienczak, MPharm, MSc (1), Adrian Cook, MSc (2), Lubbe Wiesner, PhD (1), Maxwell T. Chirehwa, MSc (1), Sarah Walker, PhD (2), Andrew Owen, PhD (3), Diana Gibb, MD, PhD (2), David Burger, PharmD, PhD (4), Helen McIlleon, PhD (1), Paolo Denti, PhD (

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; (2) MRC Clinical Trials Unit, London, United Kingdom; (3) Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom; (4) Department of Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Objective: To develop a pharmacokinetic (PK) model of nevirapine (NVP) in African children accounting for the effect of *CYP2B6* polymorphisms and diurnal variation on clearance (CL) and 1st-pass metabolism.

Methods: Data were included from children from CHAPAS 1 and 3 studies [1,2] (n=420, age 0.25-15 years) treated with NVP solid fixed-dose formulations BD according to WHO recommendations.[3,4]

NONMEM 7.3 was used to implement a semi-mechanistic well-stirred hepatic model [5]. Allometric scaling was applied to all CL and volume parameters.[6] The effect of diurnal variation and maturation were tested on intrinsic CL (CL_{int}) and pre-hepatic bioavailability (F).[7-9] Mixture modelling was used to impute missing genotypes (n=96).[10]

Simulations were used to evaluate the effect of genotype, intake time (6:00, 7:00, 8:00, 9:00 AM/PM), and dose-splitting strategies (AM/PM - D1:100/50 mg, D2:75/75 mg, D3:50/100 mg) on C_{min} and AUC.

Results: NVP PK was best described using a 1-cmpt disposition model with absorption through 2 transit cmpts[11] and elimination using hepatic extraction accounting for 1st -pass effect. NVP free fraction was assumed to be 0.4 [12] and hepatic plasma flow 50 L/h in a 70 kg person [13]. Four metaboliser groups determined by 516G>T|983T>C genotypes had the following CL_{int} (ref. WT 14.5 kg): extensive (EM) 3.27 L/h, intermediate (IM) 2.72, slow (SM) 1.65 and ultra-slow (USM) 1.04. Diurnal variation in CL_{int} was best described using a cosine function with peak amplitude of 29.2% at 12 PM. No effect of maturation on CL_{int} was detected, but age-driven differences in pre-hepatic F were found and described using an exponential model with F at birth = 58.3% and $t_{1/2F}$ = 0.64 year.

Simulations showed that depending on intake time the ratio between median C_{min} AM/PM was 1.09–1.15 and AUC 1.03–1.07. The differences in ratios between median C_{min} AM/PM for tested dose-splitting strategies were: D1 0.93, D2 1.13, D3 1.41; and AUC: 0.90, 1.04, and 1.22, respectively. C_{min_PM} <3mg/L [14] was observed in 43% of EM min_PM >7.6 mg/L.[14]

Conclusions: Simulations suggest that average C_{min} and AUC in NVP are not greatly affected by intake time, possibly due to long $t_{1/2}$. When dose cannot be split equally, larger doses should be given AM. To achieve homogenous exposures, the NVP dose for SM and USM should be reduced by 50%. Children

References:

[1] Mulenga, V. et al. Strategies for Nevirapine Initiation in HIV-Infected Children Taking Pediatric Fixed Dose Combination 'Baby Pills' in Zambia: A Randomized Controlled Trial. Clin. Infect. Dis. 51, 1081–1089

(2010).
[2] Mulenga, V. et al. Abacavir , zidovudine , or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label , parallel-group , randomised controlled trial. Lancet Infect. Dis. 3099, 1–11 (2015).
[3] World Health Organisation. Antiretroviral therapy for HIV infection in infants and children: Towards universal access. (2010). at http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf
[4] World Health Organisation. WHO recommendations on ARV medicines for treating and preventing HIV infections in younger children, technical summary. 30 Nov 2006. (2006). at http://www.who.int/hiv/paediatric/technicalsummary113006.pdf
[5] Gordi, T. et al. A semiphysiological pharmacokinetic model for artemisinin in healthy subjects incorporating autoinduction of metabolism and saturable first-pass hepatic extraction. Br. J. Clin. Pharmacol. 59, 189–98 (2005)
[6] Holford, N., Heo, Y. & Anderson, B. A Pharmacokinetic Standard for Babies and Adults. J. Pharm. Sci. 102, 2941–2952 (2013).
[7] Anderson, B. J. & Holford, N. H. G. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu. Rev. Pharmacol. Toxicol. 48, 303–32 (2008).
[8] Tomalik-Scharte, D. et al. Population pharmacokinetic analysis of circadian rhythms in hepatic CYP3A activity using midazolam. J. Clin. Pharmacol. (2014). doi:10.1002/jcph.318
[9] van Rongen, a et al. Population Pharmacokinetic Model Characterizing 24-Hour Variation in the Pharmacokinetics of Oral and Intravenous Midazolam in Healthy Volunteers. CPT Pharmacometrics Syst. Pharmacol. 4, 454–464 (2015).
[10] Keizer, R. J., Zandvliet, A. S., Beijnen, J. H., Schellens, J. H. M. & Huitema, A. D. R. Performance of methods for handling missing categorical covariate data in population pharmacokinetic analyses. AAPS J. 14, 601–11 (2012).
[11] Savic, R. M., Jonker, D. M., Kerbusch, T. & Karlsson, M. O. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J. Pharmacokinet. Pharmacodyn. 34, 711–26 (2007).
[12] Boehringer Ingelheim International GmbH. *SUMMARY OF PRODUCT CHARACTERISTICS - Viramune*.
[13] Bradley, S., Ingelfinger, F., Bradley, G. & Curry, J. The Estimation of Hepatic Blood Flow in Man. *J Clin Inves* **24,** 890–897 (1945).
[14] La Porte, C. J. L. et al. Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. Rev. Antivir. Ther. 3, 5–14 (2006).

II-22: *Roberto Bizzotto* Mixed-effect deconvolution: a new method applied to oral paracetamol absorption

Roberto Bizzotto (1), Bo Ahrén (2), Andrea Mari (1)
(1) Neuroscience Institute, National Research Council, Padova, Italy; (2) Department of Clinical Sciences, Lund University, Lund, Sweden

Objectives: The estimation of a model input by deconvolution is a complex problem which has been addressed in multiple ways [1]. Restrictive assumptions were made when employing mixed-effect methods [2]. Using data of paracetamol kinetics, we developed a new mixed-effect approach estimating the autocorrelation of non-parametric input functions and we compared its performance with a previously developed single subject deconvolution method based on regularized least square estimation.

Methods: Paracetamol plasma concentration was measured after ingestion of a tablet (1.5 g) dissolved in a liquid meal with variable composition [3]. The kinetics profiles (N=52) from 38 subjects were analysed with a two-compartmental distribution model (with typical parameter values as from the literature [4]) and a non-parametric representation of the rate of appearance of oral paracetamol (RaO). A mixed-effect implementation was developed with Monolix, in which inter-individual variability (IIV) is assumed on all parameters and RaO is the piecewise linear interpolation of log-normal parameters estimated at 10-min intervals and correlated between each other. This method (A) was compared with a single-subject implementation (B) assuming no IIV on kinetic parameters and a piecewise constant RaO with 2-min steps, determined with Matlab through regularized least square estimation with minimization of the second derivatives [5], [6].

Results: The correlation between the estimated RaO integrals was 89%. Method A produced a worse fit of the data: the coefficient of variation for the residual error was 20.6% vs 10.3%. However, the derived median bioavailability was more in line with literature values (60% to 90% [4]): 66% vs 47%. Moreover, A ensures RaO is always positive, whilst B produced negative values whose integral was 31% (median) of the positive values integral. Method A produced sharper Rao profiles: the mean number of peaks above 50 µmol/min was 2.1 vs 1.6, and the median standard deviation of the differences in RaO over 2-min intervals was 13.6 µmol/min vs 9.0 µmol/min.

Conclusions: Compared to a traditional single-subject deconvolution method, a new mixed-effect approach applied on paracetamol data revealed to be more reliable in terms of bioavailability estimation and could fit the data with always positive, although highly variable, rates of appearance. This method may prove useful in many scenarios, e.g. for the assessment of gastric emptying.

References:
[1] D. Commenges, “The deconvolution problem: Fast algorithms including the preconditioned conjugate-gradient to compute a MAP estimator,” *IEEE Trans. Autom. Control*, vol. 29, no. 3, pp. 229–243, Mar. 1984.
[2] K. E. Fattinger and D. Verotta, “A nonparametric subject-specific population method for deconvolution: I. Description, internal validation, and real data examples,” *J. Pharmacokinet. Biopharm.*, vol. 23, no. 6, pp. 581–610, Dec. 1995.
[3] W. Alsalim, A. Tura, G. Pacini, B. Omar, R. Bizzotto, A. Mari, and B. Ahrén, “Mixed meal ingestion diminishes glucose excursion in comparison with glucose ingestion via several adaptive mechanisms in people with and without type 2 diabetes,” *Diabetes Obes. Metab.*, vol. 18, no. 1, pp. 24–33, Jan. 2016.
[4] M. D. Rawlins, D. B. Henderson, and A. R. Hijab, “Pharmacokinetics of paracetamol (acetaminophen)

after intravenous and oral administration," *Eur. J. Clin. Pharmacol.*, vol. 11, no. 4, pp. 283–286, Apr. 1977.
[5] D. L. Phillips, "A Technique for the Numerical Solution of Certain Integral Equations of the First Kind," *J ACM*, vol. 9, no. 1, pp. 84–97, Jan. 1962.
[6] S. Twomey, "The application of numerical filtering to the solution of integral equations encountered in indirect sensing measurements," *J. Frankl. Inst.*, 1965.

II-23: *Henrik Bjugård Nyberg* Dismounting Saddles on the Likelihood Surface

Henrik Bjugård Nyberg[1,2], Andrew C. Hooker[1], Yasunori Aoki[1]
[1] Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden [2] Mango Solutions Ltd, Chippenham, United Kingdom

Objectives: One issue with parameter estimation in nonlinear mixed-effects models is saddle points on the likelihood surface. A saddle point is characterized by at least one eigenvector along which the objective function is at a maximum rather than a minimum. Methods that work by minimizing the gradient will not be able to distinguish saddle points from minima, and may therefore produce final parameter estimates that actually lie in saddle points. The point may be a minimum in all other directions, making it potentially hard to find a way out of the point.
In this work we propose a method that characterizes a point using the R-matrix, and based on the computed R-matrix selects new parameter values to dismount from a saddle.

Methods:

The Proposed Algorithm
The best acquired approximation of the R matrix in a point is eigen-decomposed. The lowest eigenvalue is determined, positive or negative, and the corresponding eigenvector is identified. A new set of population parameter values is then selected such that they lie along the identified eigenvector. The new parameter values are determined by finding dOFV=1 using a second order Taylor series approximation of the likelihood surface. Parameter estimation is then re-initiated.

Numerical Experiment
Two published models and datasets were selected for their stability, relative simplicity and short estimation times:
1. Jönsson et al [2]
2. Bergmann et al [3]
Initial estimates were randomly perturbed within an order of magnitude around the published parameter values. Parameter estimation was then performed using the FOCEI method in NONMEM 7.3 [2]. Our algorithm was then applied once as described above.

Results: With the first model 201 out of 1,000 estimations produced a higher OFV than the lowest known. For the second model the number was 293 out of 1,000. After applying the proposed algorithm, only 25 estimations remained with higher than minimum OFVs for model 1, and 187 remained for model 2. Some estimations were not moved by our procedure at all, which may be explained by local minima.
Our procedure caused no rise in OFV for any of the estimations.

Conclusion: We have proposed a method that efficiently reduces the issue with saddle points in parameter estimation.

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

References:
[1] Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J., NONMEM User's Guides. (1989-2014), Icon

Development Solutions, Ellicott City, MD, USA, 2014.
[2] Jönsson et al, Population pharmacokinetic modelling and estimation of dosing strategy for NXY-059, a nitrone being developed for stroke, Clinical Pharmakocinetics (2005), 44(8):863-78
[3] Bergmann et al, Impact of CYP2C8*3 on paclitaxel clearance: a population pharmacokinetic and pharmacogenomic study in 93 patients with ovarian cancer, The Pharmacogenomics Journal (2011) 11, 113–120

II-24: *Dimitra Bon* PK-PD-VK modeling for hepatitis C treatment with the CI and Generalized multiscale model.

Dimitra Bon (1) and Eva Herrmann (1)
Institute of Biostatistics and Mathematical Modeling, Department of Medicine, Goethe University, Frankfurt am Main, Germany

Objectives: PK-PD models are used to describe the behaviour of drugs and combinations of drugs in patients with chronic viral diseases like HCV. They play an important role in drug development and optimizing effectiveness (ε (t)) of antiviral therapy. New models (VK-models) were developed in order to describe the viral kinetics under treatment with direct-acting antivirals (DAAs). Clinical data with such new drugs showed a triphasic decay with a rapid first phase, a moderate second phase decay and a relatively slow third phase decay during the first few weeks. Therefore, classical biphasic models may not been suitable. The viral kinetic modeling will be based on PK-PD models.

Methods: Pharmacokinetics of the serum drug level of Sofosbuvir as well as its metabolite was modelled by Bateman function. For the pharmacodynamic model we assumed that the effect of blocking viral production does not depend directly on the serum drug level but on an intermediate compartment. Here we compare the generalized multiscale model that describes both, intracellular and cellular dynamics, with the classic biphasic model (CI). We evaluate the two models with the design of the SPARE study [1], by using a fully PK-PD model. In order to estimate the pharmacokinetic parameters, the efficacy of treatment and viral kinetic curves, data from 25 patients were fitted by maximum likelihood method individually in each patient.

Results: All patients were fitted well by both models. The estimated viral kinetic parameters (viral clearance rate, infected cells loss rate and the total treatment effect) were significant different between the two models. In contrast to the other multiscale models that use approximation solutions, the generalized multiscale model can be easily adapted for modelling full PK-PD.

Conclusions: The new variant of a multiscale model presented here is able to describe the viral kinetics of HCV in a combination with PK-PD, under these new treatments without a computational effort.

References:
[1] Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013 Aug;310(8):804{811. Available from: http://dx.doi.org/10.1001/jama.2013.109309.

II-25: *Charlotte Bon* A target mediated cellular uptake model to assess the asialogycoprotein receptor shuttle capacity in hepatocytes

Charlotte Bon (1), Erich Koller (2), Martina Mueller (2), Wouter Driessen (3), Kevin Brady (3), Franz Schuler (2), Ben-Fillippo Krippendorff (1)

(1) Quantitative and Systems Pharmacology, Pharmaceutical Sciences, pRED, Roche Innovation Center Basel, (2) Drug Disposition and Safety, Pharmaceutical Sciences, pRED, Roche Innovation Center Basel, (3) DMPK and Bioanalytical R&D, Pharmaceutical Sciences, pRED, Roche Innovation Center Basel

Objectives: GalNAc, triantennary N-acetyl galactosamine, is a high-affinity ligand to the asialoglycoproteins receptor (ASGPR) which is highly expressed at the hepatocyte cell surface [1, 2]. Therefore, ASGPR is thought to be a promising target for enhancing uptake into hepatocyte. We aim to develop an in-vitro target mediated uptake model of GalNAc conjugated antisense oligonucleotides. The model is intended to help understand the different cellular processes influencing cellular uptake of GalNAc-LNA gapmers and quantify the capacity of ASGPR as a shuttle.

Methods: We used literature information on the asialoglycoprotein receptor kinetics and ligand affinity to develop the target mediated uptake model [3, 4]. The ASGPR has been extensively scrutinized since its discovery in the mid-1970s [5] which allowed us to implement a detailed mechanistic model structure [6] in Simbiology®/Matlab®. In-vitro uptake data were obtained using primary rat hepatocytes and exposing them to different GalNAc-LNA gapmers concentrations. The data was then fitted to the uptake model and parameters were then compared to the ones found in the literature. Also a sensitivity analysis was performed allowing the identification of crucial parameters influencing the ASGPR shuttle capacity.

Results: We find that the developed uptake model allowed to quantitatively predict the dose proportional cellular uptake at low GalNAc-LNA concentrations. The ASGPR density and the ratio of internalization vs recycling rates appear to be crucial parameters. The model suggested that the uptake data can be explained when including a loss of ASGPR expression on hepatocytes over time, probably due to the in-vitro conditions.

Conclusions: Modeling the target mediated uptake due to ASGPR allowed to characterize this shuttle quantitatively and helped to understand the dynamics influencing the in-vitro cellular uptake data.

References:

[1] Weigel, P.H. and J.H. Yik, Glycans as endocytosis signals: the cases of the asialoglycoprotein and hyaluronan/chondroitin sulfate receptors. Biochim Biophys Acta, 2002. 1572(2-3): p. 341-63.
[2] Lee, Y.C., et al., Binding of synthetic oligosaccharides to the hepatic Gal/GalNAc lectin. Dependence on fine structural features. J Biol Chem, 1983. 258(1): p. 199-202.
[3] Schwartz, A.L., S.E. Fridovich, and H.F. Lodish, Kinetics of internalization and recycling of the asialoglycoprotein receptor in a hepatoma cell line. J Biol Chem, 1982. 257(8): p. 4230-7.

II-26: *Irina Bondareva* External validation and predictability of nonlinear models for changes in steady–state pharmacokinetics (PK) of carbamazepine (CBZ) and valproate (VPA) due to antiepileptic drug-drug interactions using sparse therapeutic drug monitoring (TDM) data

Irina Bondareva
The Research Institute of Physical – Chemical Medicine, Russia

Objectives: Antiepileptic drug (AED) monotherapy is preferable to polytherapy, but some patients require more than one AED for successful seizure control. Among others, potential PK drug-drug interactions of so called old AEDs are indications for TDM of AEDs. The objective of the study is to evaluate the predictability of individualized dosage regimens for CBZ and VPA given as combination therapy with other AEDs based on TDM data of epileptic patients and the earlier developed nonlinear population models for PK drug-drug interactions.

Methods: TDM data were routinely collected in the Laboratory of Pharmacokinetics of Moscow Medical University. Levels of AEDs were measured by high performance liquid chromatography. The PK analysis was performed using the USC*PACK software based on 226 TDM (peak-trough strategy) data files of adult epileptic patients who received chronic CBZ- or VAL-monotherapy or AED duotherapy. This study included epileptic patients with long and rich TDM stories: repeated measurements during 1 – 2 years related to modifications in dosages and/or addition of AED to monotherapy. These data were not included in the population models. In the nonlinear models of heteroinduction, the metabolic rate asymptotically changes from a monotherapy value (D) during time-lag (Lambda) to a value (D+A) after heteroinduction. The prediction errors were estimated as the difference between observed levels after changes in AED dosage regimen and those predicted based on the patient-specific Bayesian posterior PK model and the TDM data before changes.

Results: Absolute value of prediction error was less or equal to 25% and considered as “acceptable” in 42 (75%) cases for CBZ-monotherapy group, 40 (76.9%) for VPA-monotherapy, in 35 (72.9%) for CBZ+VPA, in 24 (66.7%) for VPA+CBZ, and in 22 (64.7%) for CBZ+AED. Intraindividual variability of predictions varied from 23 - 25% for monotherapy to 26 – 28% for polytherapy. No tendency to overestimate or underestimate the concentration levels was observed.

Conclusions: This study has demonstrated that, in most cases, predictions of future AED concentrations based on the population PK models, supplemented by TDM data and patient-specific Bayesian posterior parameter modelling provided clinically acceptable estimates. The individual prediction errors were slightly higher for changes in polytherapy compared to monotherapy, which highlights the value of TDM and individualizing AED dosage regimen in the setting of polypharmacy.

II-27: *Jennifer Bonner* Building of virtual geriatric cancer populations for physiologically-based pharmacokinetic modelling and simulation in cancer patients greater than 70 years of age

Jennifer J. Bonner (1), Nicola Hannaway (2), Nicola Wyatt (2), Yvette Drew (1,2), Alastair Greystoke (1,2)
(1) Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK; (2) Freeman Hospital, The Newcastle upon Tyne NHS Trust, Newcastle upon Tyne, United Kingdom

Objectives: Although the elderly comprise the majority of cancer patients (1), they are under-represented in clinical trials of anticancer agents (2,3), particularly in the Phase I trials where doses are determined. This may be one of the reasons why they have higher rates of side-effects. Physiologically-based pharmacokinetic (PBPK) modelling and simulation may assist in dose selection and exposure prediction in these patients but requires a virtual geriatric population with realistic information on parameters that change with advancing age and the presence of cancer.
Whether physiological changes that potentially affecting PK may change with cancer type as well as with age is not known. Therefore we assessed basic parameters that would impact on PBPK modelling in non-small cell lung and ovarian cancer patients over the age of 70 years and compared them to simulated healthy individuals in the same age range.

Methods: Anonymised patient data was obtained from 228 non-small cell lung cancer patients and 113 patients with ovarian cancer. Relationships between height and age, weight and height, and glomerular filtration rate (GFR) and age were assessed by nonlinear regression. The slope and intercept values from the height and weight curves were used to simulate height and weight values for 1,000 virtual geriatric subjects within Simcyp version 14.1. Comparisons of patient GFR, serum albumin, and haematocrit by cancer type were performed by one-way ANOVA with Tukey's multiple comparisons test.

Results: GFRs were significantly lower in the ovarian cancer group than in the lung cancer group (mean 57.49 mL/min vs. 67.68 mL/min, $p<0.001$) as were albumin concentrations (mean 36.87 g/L vs. 39.17 g/L, $p<0.01$) and haematocrits (mean 0.36 vs. 0.38, $p<0.01$). All laboratory parameters were significantly different from simulated healthy individuals. As expected an inverse linear relationship between age and GFR was observed for both the lung and ovarian cancer groups.

Conclusions: These results show that laboratory parameters that may significantly affect PK differ significantly in cancer patients from simulated healthy individuals of the same age, and may also differ by cancer type. These findings underscore the need for cancer type-specific virtual populations for modelling and simulation in elderly patients with cancer.

References:
[1] Talarico, L., G. Chen, and R. Pazdur, Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the US Food and Drug Administration. Journal of Clinical Oncology, 2004. 22(22): p. 4626-4631.
[2] Hutchins, L.F., et al., Underrepresentation of patients 65 years of age or older in cancer-treatment trials. The New England Journal of Medicine, 1999. 341(27): p. 2061-2067.
[3] Murthy, V.H., H.M. Krumholz, and C.P. Gross, Participation in cancer clinical trials: race-, sex-, and age-based disparities. Journal of the American Medical Association, 2004. 291(22): p. 2720-2726.

II-28: *Elisa Borella* Development and integration of the WinBUGS connector in the DDMoRe Interoperability Framework

Cristiana Larizza (1), Elisa Borella (1), Lorenzo Pasotti (1), Gareth Smith (2), Richard Kaye (3), Paolo Magni (1)

(1) Department of Electrical, Computer and Biomedical Engineering, University of Pavia, via Ferrata 5, Pavia, I-27100, Italy; (3) Cyprotex Discovery Ltd; (4) Mango Solutions.

Objectives: The objective of our work is to develop and test a connector integrating WinBUGS [1] in the DDMoRe Interoperability Framework platform. The connector allows the user to perform all the steps of a WinBUGS model execution (PharmML into WinBUGS model translation, WinBUGS run, generation and retrieval of the desired output) within the DDMoRe Interoperability Framework platform.

Methods: Connector development includes five steps: 1) Upgrade of our previously developed PharmML-to-WinBUGS model and NMTRAN-to-BUGS data file translation tools [2] to include new features (i.e., Bayesian priors) available in PharmML 0.7 and successive versions [3]. 2) Support to categorical covariates, piecewise function definition and correlation of random effects, which were not included in the previous version of the translator. 3) Implementation of a Java-based tool for standardized output (SO) file creation, summarizing the outputs of a WinBUGS run (CODA files), using lib-PharmML-SO [4]. 4) Development of a connector, via different shell scripts, that is responsible for: preparing inputs, invoking the tool, monitoring the progress of the processing and retrieving results from execution. 5) Definition of interoperability commands in the form of R functions to define the number of Markov chains, the number of total iterations per chain, the length of burn-in and other common options in Bayesian analysis. PharmML 0.8, WinBugs 1.4.3, BlackBox 1.5, PKPD Model Library 1.2, the WBDiff and WBDev interfaces and Java Libraries available in [5] were used.

Results: The connector was successfully tested on a variety of algebraic/ODEs single-subject/population models publicly available on the DDMoRe Model Repository [6]. For testing purposes, priors were properly added when not present to enable Bayesian estimation.

Conclusions: The connector allows the user to specify the quantities to be monitored, customize the MCMC sampling algorithm, run the execution, retrieve the standardized output, and perform graphical convergence diagnostics and posterior inference for a large number of modelling situations within the DDMoRe Interoperability Framework. Together with the Model Repository, it promotes the exchange and reusability of models in Bayesian framework, which could greatly improve drug development.

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

References:

[1] www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/
[2] PAGE 24 (2015) Abstr 3565 [www.page-meeting.org/?abstract=3565]
[3] Swat MJ et al. Pharmacometrics Markup Language (PharmML): Opening New Perspectives for Model Exchange in Drug Development. CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 316-319.
[4] PAGE 24 (2015) Abstr 3599 [www.page-meeting.org/?abstract=3599]
[5] sourceforge.net/p/ccopi/code/ci/master/tree/
[6] repository.ddmore.eu

II-29: *Agnieszka Borsuk* Population pharmacokinetics of sufentanil after epidural and intravenous administration in children and infants

Agnieszka Borsuk (1), Bogumiła Wołoszczuk-Gębicka (2), Alicja Bartkowska-Śniatkowska (3), Agnieszka Bienert (4), Paweł Wiczling (1)

(1) Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Poland, (2) Chair of Medical Lifesaving , Faculty of Medicine, University of Rzeszow, Poland, (3) Department of Pediatric Anesthesiology and Intensive Therapy and Pain, Poznań University of Medical Sciences, Poland, (4) Department of Clinical Pharmacy and Biopharmacy, Poznań University of Medical Sciences, Poland

Objectives: Sufentanil is a potent opioid widely used in anesthetic and intensive care management. Literature data describing pharmacokinetics of sufentanil in pediatric population are limited, while the clinical use of sufentanil increases in this population. The aim of this study was to develop a population model describing pharmacokinetics of sufentanil administered via intravenous and epidural infusion in children and infants.

Methods: Patients from two previous studies were included in the analysis: 41 children 0 -18 years old receiving intravenous sufentanil infusion [1] and 20 infants 3–36 months old receiving epidural sufentanil infusion [2]. Population pharmacokinetic analysis was conducted using non-linear mixed effects modelling in NONMEM 7.3.0 software. Allometric scaling with theoretical exponents was implemented to account for changes in body size. Changes in metabolic clearance due to maturation of enzyme activity were characterized as a fraction of adult clearance by Hill equation. Model selection was guided by the change in objective function value (OFV) and diagnostic plots, including visual predictive checks. Precision of parameter estimates was assessed by nonparametric bootstrap.

Results: A two-compartment model with first-order absorption sufficiently described sufentanil pharmacokinetics. Typical values of the central and peripheral volume of distribution, metabolic and inter-compartmental clearance for a theoretical patient of 70 kg weight were as follows: VC =7.08 L, VT = 474.52 L, Cl = 49.06 L/hr, and Q = 41.79 L/hr. The effect of body weight on disposition PK parameters was well accounted for by allometric scaling with theoretical exponents. The typical value of absorption rate constant from epidural space was 0.05/h. The values of Hill coefficient and postmenstrual age at which enzyme activity is 50% of the mature value were 2.73 and 32 weeks respectively. The inter-individual variability was estimated for CL, VT, and Q.

Conclusions: Population pharmacokinetic model was successfully developed to describe the time course and variability of sufentanil concentrations in children and infants. The model suggests slow absorption of sufentanil administered via epidural infusion. However, estimated absorption rate constant is based on sparse data. Future work will focus on including additional patients receiving sufentanil via epidural infusion with more dense sampling schedule.

References:

[1] Bartkowska-Śniatkowska A, Bienert A, Wiczling P, et al. Pharmacokinetics of sufentanil during long-term infusion in critically ill pediatric patients. J Clin Pharmacol 2016; 56: 109–15.
[2] Woloszczuk-Gebicka B, Grabowski T, Borucka B, Karas-Trzeciak M. Pharmacokinetics of sufentanil administered with 0.2% ropivacaine as a continuous epidural infusion for postoperative pain relief in infants. Paediatr Anaesth 2014; 24: 962–7.

II-30: *Margreke Brill* Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug resistant tuberculosis

Margreke J.E. Brill (1), Elin M. Svensson (1), Mishal Pandie (2), Gary Maartens (2), Mats O. Karlsson (1)
(1) Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Objectives: Cytochrome P450 3A4 (CYP3A4) inhibitors lopinavir/ritonavir or the moderate CYP3A4 inducer nevirapine may affect the exposure of the anti-tuberculosis drug bedaquiline and its metabolite M2. In this work we aimed to quantify lopinavir/ritonavir and nevirapine drug-drug interaction effects on bedaquiline and M2 in patients co-infected with HIV and multidrug resistant tuberculosis (MDR-TB) using population pharmacokinetic (PK) analysis. The results were compared to model-based predictions from single-dose studies in subjects without tuberculosis.

Methods: An observational PK study was performed in three groups of MDR-TB patients during the bedaquiline maintenance dosing period: HIV-seronegative patients without antiretroviral treatment (ART) and HIV-infected patients using ART regimens containing either lopinavir/ritonavir or nevirapine. Bedaquiline and M2 samples were collected over 48 hours after a 200 mg dose [1]. A previously developed population PK model for patients was used as prior information to inform parameter estimation using the NWPRI functionality in NONMEM 7.3 [2,3]. The uncertainty of the model parameters were calculated using SIR [4].

Results: The final model was able to describe bedaquiline and M2 concentrations well for all three groups and the PK parameters estimates were close to their prior values. Lopinavir/ritonavir co-administration reduced bedaquiline clearance substantially to 25% (95% confidence interval, 17 - 35%) and M2 clearance to 59% (44 - 69%) of their original values. Nevirapine co-administration altered bedaquiline clearance to 82% (67 - 99%) and M2 clearance to 119% (95 - 156%) of their original values.

Conclusions: This work confirms earlier model-based prediction of lopinavir/ritonavir and nevirapine interaction effects on bedaquiline and M2 clearance from single-dose studies for MDR-TB and HIV co-infected patients receiving long-term treatments [3]. To normalize bedaquiline exposure in patients with concomitant lopinavir/ritonavir therapy, an adjusted bedaquiline dosing regimen is proposed.

References:

[1] Pandie, M. *et al.* Drug–drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J. Antimicrob. Chemother.* dkv447 (2016). doi:10.1093/jac/dkv447
[2] Svensson, E. M., Dosne, A.-G. & Karlsson, M.O. Population pharmacokinetics of bedaquiline and metabolite M2 in drug-resistant tuberculosis patients – the effect of time-varying weight and albumin. (Submitted).
[3] Svensson, E. M., Dooley, K. E. & Karlsson, M. O. Impact of Lopinavir-Ritonavir or Nevirapine on Bedaquiline Exposures and Potential Implications for Patients with Tuberculosis-HIV Coinfection. *Antimicrob. Agents Chemother.* **58,** 6406–6412 (2014).
[4] Dosne, A.-G., Bergstrand, M. & Karlsson, M. O. Application of Sampling Importance Resampling to estimate parameter uncertainty distributions. PAGE (2013).

Acknowledgements: MP acknowledges funding in the form of a FIDSSA-GSK Research Fellowship and a Discovery Foundation Academic Fellowship Award. GM was supported in part by the National Research Foundation of South Africa (grant specific unique reference numbers 85810 and 90729, respectively). ES and MK were supported by the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) (grant agreement 115337 to ES and MK) for the PreDiCT-TB consortium.

II-31: *Hannah Britz* Physiologically-Based Pharmacokinetic (PBPK) Modeling of the Dronedarone Drug-Drug Interaction with Digoxin

Hannah Britz (1), Daniel Moj (1), Nina Hanke (1) and Thorsten Lehr (1)
(1) Clinical Pharmacy, Saarland University, Saarbruecken, Germany

Objectives: Dronedarone is the strongest known perpetrator drug to evaluate the impact of P-gp inhibition on P-gp substrates (victim drugs) during co-administration[1]. Our objective was to establish a PBPK model of dronedarone to explore and predict the drug-drug interactions (DDIs) of dronedarone with P-gp substrates.

Methods: A PBPK model of dronedarone was built in PK-Sim® (version 6.0.3) and MoBi® (version 6.0.3). Drug-dependent parameters (e.g. logP, solubility) as well as concentration-time profiles (intravenous (iv) and oral (po) administration) and population data (e.g. age, weight) from clinical studies with dronedarone were obtained from literature. During model development, parameters, for which no information was available, were optimized to describe observed concentration-time profiles, followed by model evaluation (prediction of concentration-time profiles) and coupling of the dronedarone model with a previously developed digoxin model.

Results: Dronedarone inhibits its own metabolism through a mechanism-based inhibition (MBI) of CYP3A4. This MBI is extremely relevant for the description of the dronedarone PK after oral administration, because it leads to complete inhibition of CYP3A4 in the duodenal mucosa already at low doses of dronedarone. In contrast, the CYP3A4 MBI in the liver shows time- and dose-dependency. For simulation of the DDI the models of dronedarone and digoxin were coupled and a 1.26-fold increase of digoxin area under the curve (AUC) during dronedarone treatment was predicted. In clinical studies a 2.6-fold increase of digoxin AUC under dronedarone co-medication has been observed[2].

Conclusions: With the PBPK model of dronedarone the hypothesis of MBI as a relevant mechanism for the PK of dronedarone gets further support. To refine the prediction of the dronedarone-digoxin model, the PBPK model of dronedarone could be extended to include its main metabolite N-debutyldronedarone as an additional P-gp inhibitor.

References:
[1] U.S. Department of Health and Human Services, FDA, Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. 2012.
[2] Kumi R, Garnett C, Gobburu J, Marroum P. Clinical Pharmacology and Biopharmaceutics Review – Application number: 22-425. 2006.

II-32: *Jantine Brussee* Predictive performance of a CRP and organ failure based pharmacokinetic model for midazolam in critically ill children across external datasets in neonates, children and adults

Janneke M. Brussee (1), Nienke J. Vet (2), Pyry A.J. Välitalo (1), Elke H.J. Krekels (1), Mariska Y. Peeters (3), Abraham J. Valkenburg (4), Evelyne Jacqz-Aigrain (5), Joop M.A. van Gerven (6), Matthijs de Hoog (2), Saskia N. de Wildt (4), Catherijne A.J.

(1) Division of Pharmacology, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands, (2) Department of Pediatrics, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands, (3) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands, (4) Department of Pediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands, (5) Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Paris, France, (6) Centre for Human Drug Research, Leiden, the Netherlands

Objectives: Midazolam is often used for sedation in pediatric intensive cares and for surgical procedures. A recent study quantified the effect of inflammation and organ failure on midazolam clearance in critically ill term neonates and children [1]. This project aims to evaluate the predictive performance of this recently developed model across a wide range in (preterm) neonatal, pediatric and adult populations.

Methods: Concentration predictions by the population pharmacokinetic model for midazolam in which CRP concentrations and organ failure are taken into account [1], were evaluated in n=55 preterm neonates [2,3], n=18 critically ill children [4], n=26 children undergoing open-heart surgery [5], n=24 children undergoing craniofacial surgery [6], n=6 pediatric oncology patients [7], and n=20 healthy adults [8]. In total n=149 subjects (aged 1 day - 31 years, body weight 0.77 - 89 kg) receiving intravenous midazolam were included. In case of missing covariate values (i.e. CRP concentrations [2,3,6-8]), typical values without covariate effects were assumed.

Results: The model predictions were adequate for critically ill children [4] and children undergoing open-heart surgery [5] (median prediction error (MPE) 14% and -3.1% respectively). In the pediatric oncology patients [7], overall MPE was 50.2% and the trough concentrations were more accurately predicted than the peak concentrations. For patients undergoing craniofacial surgery [6], plasma concentrations were overpredicted (MPE -250%). In preterm neonates [2,3], the plasma concentrations were underpredicted (MPE 63.5 and 68.2%). In the densely sampled adult study [8], a trend in residuals over time (CWRES) was apparent, with under- and overprediction of the peak and trough concentrations, respectively.

Conclusions: Based on the data from these 7 studies, it can be concluded that the model cannot be used for direct extrapolation to other populations such as preterm neonates and adults. However, for critically ill children in the same age and body weight range as the subjects in the learning dataset and to a lesser extent for children undergoing surgical procedures, midazolam plasma concentrations could be accurately predicted.

References:

[1] Vet NJ, Brussee JM, *et al*. 2016 Am J Respir Crit Care Med. 2016 Jan 21
[2] De Wildt SN *et al*. Clin Pharmacol Ther. 2001 Dec; 70(6):525-31
[3] Jacqz-Agrain E *et al*. Lancet. 1994 Sep; 344(8923):646-50
[4] De Wildt SN *et al*. Critical care medicine. 2003 Jul;31(7):1952-8
[5] Valkenburg AJ *et al*. Pain. 2011 Sep;152(9):2059-64

[6] Peeters MY *et al*. Anesthesiology. 2006 Dec; 105(6):1135-46
[7] De Wildt SN *et al*. Clin Pharmacol Ther. 2000 Mar;67:104
[8] Van Gerven JM *et al*. Br J Clin Pharmacol. 1997 Nov; 44(5):487-93

II-33: *Vincent Buchheit* Added value of the Data Scientist role in a Clinical Pharmacometric group

Vincent Buchheit, Nicolas Frey
Hoffmann La Roche

Objective: The objective of this poster is to describe the current role of the Clinical Pharmacology Data Scientist (CPDS) within Roche pRED and to illustrate how this role enables efficient quantitative clinical pharmacology activities.

Methods: The Clinical Pharmacometrics (CPM) group at Roche pRED consists of Pharmacometrician (PHME) and CPDS. One of the main objectives of each CPM group, within the pharmaceutical industry, is to provide impactful modeling and simulation (M&S) inputs to clinical project [1] [2] and the PHME main accountabilities are to define the M&S strategy, perform the work and communicate the results. The CPDS main accountabilities are to provide ready to use modeling input files from different sources, conduct data exploration, integrate important information into graphics easy to read, use previously developed models to identify and fix (if possible) data inconsistencies [3] [4], perform simulations, produce outputs for reports, etc.

Results: Over the past few years, we have established a group of 9 CPDS, which supports M&S activities at the study, project and disease levels. Based on our experience, a CPDS free up time of a PHME around 30 to 40% allowing for more M&S activities to be conducted. Therefore, our recommendation to maximize the efficiency of a CPM group, is to have a ratio of at least one 1 CPDS for 2.5 PHME. With usually a Master degree in computational science and engineering, a CPDS brings flexibility and efficiency in the analysis process, increase the quality of the deliverables and also ensure full traceability and reproducibility. The most significant improvement is in the reduction of the time between clinical database lock and dataset ready for analysis which is usually around 70%. The efficiency of a CPDS is further increased when prior models have been developed and can then be used by the CPDS to further assess the data quality and initiate data interpretation. Some examples of deliverables and associated impacts will be shown.

Conclusions: In order to provide impactful inputs to clinical project, Pharmacometricians have to deliver high quality works on time. Performing effectively requires many skills that not all Pharmacometricians have. It is therefore essential to work in collaboration with data scientist to maximize quality and efficiency of the m&s analysis.

References:

[1] FDA, March 2004: Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
[2] Aarons, L. et al., Role of modelling and simulation in Phase I drug development.
[3] Buchheit, V. et al., Efficient quality review for modeling input dataset, PAGE 20 (2011) Abstr 2041 [www.page-meeting.org/?abstract=2041]
[4] Buchheit, V. and Frey, N., Data quality impacts on modeling results, PAGE 22 (2013) Abstr 2749 [http://www.page-meeting.org/default.asp?abstract=2749]

II-34: *Charles Burdet* Joint modeling of plasma and fecal moxifloxacin pharmacokinetics in healthy volunteers

Charles Burdet (1,2), Thu Thuy Nguyen (1), Jean de Gunzburg (3), Annie Ducher (3), Marion Ghidi (3), Xavier Duval (1,2), Marina Varastet (3), Antoine Andremont (1,2), France Mentré (1,2)
(1) INSERM & Paris Diderot University, UMR 1137, Paris, France; (2), AP-HP, Bichat Hospital, Paris, France; (3) Da Volterra, Paris, France

Objectives: Antibiotic administration leads to fecal microbiota disruption with emergence of antimicrobial resistance [1]. Animal data suggest that emergence of bacterial resistance can be predicted from fecal antibiotic exposure [2]. We developed a joint model of plasma and fecal pharmacokinetics of the fluoroquinolone antimicrobial moxifloxacin after oral administration in humans.

Methods: Fourteen healthy volunteers were recruited in a randomized clinical trial (sponsor Da Volterra) and received a 5-day course of moxifloxacin. Moxifloxacin dosing regimen (400 mg OAD) was similar to that usually administered in infected patients. Moxifloxacin plasma concentrations were determined at D1 and D5. Eleven fecal samples were obtained from D1 to D16 for measures of moxifloxacin concentrations. Nonlinear mixed-effects modeling was performed to characterize the pharmacokinetic properties of moxifloxacin and its fecal excretion. Model selection was performed by visual inspection of various goodness of fit plots and the Bayesian Information Criteria. Analysis was performed using the SAEM algorithm and the Monolix software (Lixoft, France) [3].

Results: Moxifloxacin plasma concentrations were best described by a 2 compartment model with first order absorption and linear elimination, with a lag time. Fecal concentrations were modeled using a transit compartment between plasma and feces. Goodness-of-fit of this model was satisfactory. Median (min-max) AUC of fecal moxifloxacin was 662 µg.d/g (412-1731).

Conclusions: We developed the first joint model of moxifloxacin pharmacokinetics in plasma and feces. The administration of moxifloxacin modifies the composition of the fecal microbiota, as it was shown for other antimicrobials [4, 5]. This might allow for resistant strains or other pathogenic bacteria to colonize the gut. The modeling of bacterial counts is thereby necessary.

References:

[1] Andremont A. Commensal Flora May Play Key Role in Spreading Antibiotic Resistance. ASM News **2003**; 69(12): 601-7.
[2] Nguyen TT, Guedj J, Chachaty E, de Gunzburg J, Andremont A, Mentre F. Mathematical modeling of bacterial kinetics to predict the impact of antibiotic colonic exposure and treatment duration on the amount of resistant enterobacteria excreted. PLoS Comput Biol **2014**; 10(9): e1003840.
[3] Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. Comput Statist Data Anal **2005**; 49: 1020-38.
[4] Fantin B, Duval X, Massias L, et al. Ciprofloxacin dosage and emergence of resistance in human commensal bacteria. J Infect Dis **2009**; 200(3): 390-8.
[5] Michea-Hamzehpour M, Auckenthaler R, Kunz J, Pechere JC. Effect of a single dose of cefotaxime or ceftriaxone on human faecal flora. A double-blind study. Drugs **1988**; 35 Suppl 2: 6-11.

II-35: *Elisa Calvier* Allometric scaling of clearance in paediatrics: when does the magic of 0.75 fade?

Calvier EAM (1), Krekels EHJ (1), Välitalo PAJ (1), Rostami-Hodjegan A (2), Tibboel D (3), Danhof M (1), Knibbe CAJ (1,4)

(1) Division of Pharmacology, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands, (2) Manchester Pharmacy School, University of Manchester, Manchester, UK, (3) Intensive Care and Department of Pediatric Surgery, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, The Netherlands, (4) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

Objectives: Allometric scaling on the basis of bodyweight raised to the power of 0.75 (AS) [1] is frequently used to scale size-related changes in plasma clearance (CLp) from adults to children. A systematic assessment of its applicability is undertaken for drugs cleared through hepatic metabolism or glomerular filtration (GF).

Methods: A physiologically-based pharmacokinetic (PBPK) simulation workflow was developed in R for 12620 hypothetical drugs. In one scenario, only size-related changes in liver weight, hepatic blood flow, and glomerular filtration rate were included in simulations of 'true' paediatric CLp [2]. In a second scenario, also maturation in unbound microsomal intrinsic clearance (CLint,mic), plasma protein concentration [2], and haematocrit [3] were included in these simulated 'true' paediatric CLp values. For the first scenario, an allometric exponent was estimated based on 'true' CLp, while for both scenarios, the prediction error (PE) of AS-based paediatric CLp predictions was assessed.

Results: In the first scenario, the estimated allometric exponent ranged from 0.50 to 1.20 depending on age and drug properties, with PE of AS-based paediatric CLp predictions reaching up to 253% in neonates. In the second scenario, the PE sensitivity to drug properties and maturation was higher in the youngest children, with AS resulting in accurate CLp predictions above five years of age.

Conclusions: Using PBPK principles, it was shown that there is no evidence for one unique allometric exponent in paediatrics, even in scenarios that only consider size-related changes. As PE is most sensitive to the exponent, drug properties and maturation in younger children, AS leads to increasingly worse predictions with decreasing age.

References:

[1] Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. *Clin. Pharmacokinet. (1997)* 33(5):313–27

[2] Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin. Pharmacokinet.* (2006) 45(9):931–56

[3] Irwin JJ, Kirchner JT. Anemia in children. *Am. Fam. Physician. (*2001) 64(8):1379–86

II-36: *Tim Cardilin* Extending the Tumor Static Concentration curve to average doses – a combination therapy example using radiation therapy

Tim Cardilin (1, 2), Astrid Zimmermann (3), Mats Jirstrand (2), Joachim Almquist (2,4), Samer El Bawab (5), and Johan Gabrielsson (6)

(1) Department of Mathematical Sciences, Chalmers University of Technology and Gothenburg University, Gothenburg, Sweden, (2) Fraunhofer-Chalmers Centre, Gothenburg, Sweden, (3) Merck, Translational Innovation Platform Oncology, Darmstadt, Germany, (4) Systems and Synthetic Biology, Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden, (5) Merck, Global Early Development - Quantitative Pharmacology, Darmstadt, Germany, (6) Division of Pharmacology and Toxicology, Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden

Objectives: The recently developed concept of Tumor Static Concentration (TSC) is a valuable modeling tool for the quantitative analysis of combination therapies [2]. Here, we set out to extend TSC to situations where (average) doses are known but drug exposure data is not available.

Methods: Data consisted of Patient-Derived xenografts from combination therapy studies using ionizing radiation and a probe compound. Modelling was based on a Tumor Growth Inhibition (TGI) model [3] modified for radiation treatment. Model parameters were estimated using a mixed-effects approach implemented in Mathematica 10 [1]. A TSC-like curve was derived from tumor stasis assumptions where one of the plasma concentrations was replaced with average radiation dose over time.

Results: Drug exposure of the probe compound was successfully modeled using a one compartment exposure model. Initial attempts to model the combination efficacy data were not able to explain the effect from the combination arm. The TGI model was subsequently modified to account for potential interaction effects between the probe compound and radiation treatments. The radiation treatment-modified TGI model was then used to derive a TSC-like curve that determines all pairs of radiation doses and drug concentrations for which the tumor is kept in stasis. This curve exhibits significant curvature, reflecting the synergistic effects of administering the radiation therapy and drug together. The TSC-like curve can be used to improve the administration schedule of the treatment.

Conclusions: A model-based method for evaluation of anticancer combination therapy was extended from the use of tumor static plasma concentrations to also include average drug doses. Although used for radiation therapy in this example, the method can also be applied for regular compounds when drug exposure data is not available.

References:

[1] Almquist J, Leander J, Jirstrand M. Using sensitivity equations for computing gradients of the FOCE and FOCEI approximations to the population likelihood. J Pharmacokinet Pharmacodyn (2015) 42: 191-209.
[2] Cardilin T, Sostelly A, Gabrielsson J, El Bawab S, Amendt C, Jirstrand M. Modelling and Analysis of Tumor Growth Inhibition for Combination Therapy using Tumor Static Concentration Curves. PAGE 24 (2015) Abstr 3568 [www.page-meeting.org/?abstract=3568].
[3] Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, Germani M, Poggesi I, Rocchetti M. Predictive Pharmacokinetic-Pharmacodynamic Modeling of Tumor Growth Kinetics in Xenograft Models after Administration of Anticancer Agents. Cancer Res., (2004) 64:1094-1101.

II-37: *Luzelena Caro* Population Pharmacokinetics Modeling Characterizes the Higher Grazoprevir Exposure in Japanese Compared to Non-Japanese HCV-Infected Patients

Luzelena Caro(1), Jongtae Lee(2), Ed Feng(1), Bei Yang(2), Sunny Chapel(2), Julie Stone(1), Larissa Wenning(1)

(1) Merck & Co., Inc., Kenilworth, NJ (2) Ann Arbor Pharmacometrics Group, Ann Arbor, Michigan

Objectives: To use population PK modeling to characterize the effect of Japanese ethnicity on the non-linear plasma pharmacokinetics of grazoprevir, a component of the Zepatier™ combination approved HCV treatment, and to simulate the pharmacokinetics of various Japanese HCV patient subpopulations in order to predict PK/PD relationships in Japanese patients.

Methods: PK data in Japanese subjects obtained from one Phase 1 study and one Phase 2 and 3 study together with PK data in non-Japanese subjects from 7 Phase 1 and 12 Phase 2/3 studies were included in the population PK modeling. Japanese grazoprevir plasma concentrations were fitted to a pharmacokinetic model using non-linear mixed-effects modeling implemented in NONMEM V7 [1]. Empirical Bayes estimates of steady-state grazoprevir PK exposure (AUC_{0-24}) for Japanese patients in the Phase 2 and 3 studies were used to assess exposure in various Japanese patient subpopulations.

Results: The Japanese non-linear and greater than dose-proportional grazoprevir PK profiles were well-characterized by the grazoprevir two-compartment population PK model with first-order elimination, two parallel first-order oral absorption pathways, and dose-dependent apparent clearance, apparent volume of distribution, and distribution rate constants. These results demonstrate that Japanese ethnicity is a significant covariate for apparent clearance but not for apparent volume of distribution or distribution rate constants. The final PK model allowed simulation of the once-daily administration of grazoprevir (when administered together with elbasvir, the other component of Zepatier™) in Japanese HCV patients. The results demonstrate that steady-state grazoprevir AUC in Japanese HCV patients is estimated to be ~2-fold higher than that for non-Japanese HCV patients. The simulations also suggest that body weight, age, gender, and cirrhosis did not have a clinically relevant effect on grazoprevir steady-state AUC_{0-24}, resulting in less than a 75% increase in grazoprevir exposure in Japanese HCV patients.

Conclusions: Modeling and simulation of grazoprevir pharmacokinetics in Japanese HCV Patients suggest that the higher exposure observed compared to non-Japanese patients is attributed to reduced apparent clearance. The exposure changes in Japanese subpopulations (e.g., elderly, female, low body weight) are not expected to be clinically relevant.

References:

[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.

II-38: *Letizia Carrara* Methods and tools for multiscale modelling in Systems Pharmacology: a review

Borella Elisa, Carrara Letizia, Lavezzi Silvia Maria, Massaiu Ilaria, Sauta Elisabetta, Tosca Elena Maria, Vitali Francesca, Zucca Susanna, Pasotti Lorenzo, De Nicolao Giuseppe, Magni Paolo
Department of Electrical, Computer and Biomedical Engineering, University of Pavia, via Ferrata 5, Pavia, I-27100, Italy.

Objectives: Systems Pharmacology aims to quantitatively study the dynamic interactions between drugs and biological systems by integrating models and data at different scales, to understand how the interrelated behaviour of individual constituents (modelled, e.g., via biological networks) and the behaviour of the whole system (modelled, e.g., via PBPK models) mutually interact[1,2]. The objective of this work is to present and discuss: how models at different scales can be coupled; the types of data that can be used; the tools supporting the implementation; the practical research and drug development studies the models were built for.

Methods: Three main methods for coupling PBPK models and biological networks were identified: i) indirect/direct coupling with dynamic Flux Balance Analysis[3], ii) combination of PBPK and networks ODEs[4-8], iii) integration of genetic information as covariate[9]. Tools and languages used[3-9] are: PK-Sim and MoBi[3,9-11], GNU MCSim[6,8,12], Matlab[9,13], Insilico discovery[4,14], COPASI[5,15], SBML[6,8,16], BioTRaNS[7,17].

Results: Method i) describes both how the PBPK model affects the network and how processes at the cellular level influence distribution of compounds at the whole body scale[3]. This approach is used to study hyperuricemia therapy, ammonia detoxification and paracetamol-induced toxication, with the support of clinical data and physiological information.
For method ii), the connection is provided by network exchange rates (often related to the liver) affecting the PBPK model concentrations. Models built with this approach are used to: predict hepatotoxicity upon treatment with acetaminophen[4], predict GSH metabolism and paracetamol toxicity[5] (both on the basis of literature and in vitro data) and study chemicals interactions[6-8].
Following method iii), in[9] genetic information is included as a covariate for tissue-specific transporter-activity. Data ranging from preclinical characterizations of enzymes and proteins to safety events rates supported the building of a PBPK model for the prediction of myopathy rates.

Conclusions: The main challenges of systems pharmacology are multiscale modelling and vertical integration of heterogeneous data, for which guidelines are still missing. Here, methods and tools to face such challenges are presented, showing promising results (and limits) in practical applications.

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

References:
1] *Systems Pharmacology: Bridging Systems Biology and Pharmacokinetics-Pharmacodynamics (PKPD) in Drug Discovery and Development*.P.H. Van der Graaf and N. Benson.Pharm Res, 28, 1460-1464, 2011.
[2] *Systems Clinical Pharmacology*. A.J. Atkinson Jr and P.M. Lyster. ClinPharmacolTher, 88 (1), 3-6, 2010.
[3] *Integrating Cellular Metabolism into a Multiscale Whole-Body Model*. M. Krauss, S. Schaller, S. Borchers, R. Findeisen, J. Lippert, L. Kuepfer.PLOS Comp Biol, 8 (10), 1-13, 2012.
[4] *A multiscale modeling framework for individualized, spatiotemporal prediction of drug effects and*

toxicological risk.J.G. Diaz Ochoa, J. Bucher, A. R. R. Péry, J. M. ZaldivarComenges, J. Niklas and K. Mauch.Frontiers in Pharmacology, 3 (204), 1-11, 2013.
[5] *Multiscale modelling approach combining a kinetic model of glutathione metabolism with PBPK models of paracetamol and the potential glutathione-depletion biomarkers ophthalmic acid and 5-oxoproline in humans and rats*. S. Geenen, J. W. T. Yates, J. G. Kenna, F. Y. Bois, I. D. Wilson and H. V. Westerhoff. IntegrBiol, 5, 877-888, 2013.
[6] *Physiologically Based Modelling and Prediction of Drug Interactions*. F.Y. Bois. Basic ClinPharmacolToxicol, 106, 154-161, 2009.
[7] *Integration of PBPK and Reaction Network Modelling: Predictive Xenobiotic Metabolomics*. R. S. H. Yang, A. N. Mayeno, K. H. Liao, K. F. Reardon and B. Reisfeld.ALTEX 22, Special Issue 2, 373-379, 2005.
[8] *A mechanistic modeling framework for predicting metabolic interactions in complex mixtures*. S. Cheng, F.Y. Bois. Environmental health perspectives, 119(12), 1712-1718, 2011.
[9] *A Mechanistic, Model-Based Approach to Safety Assessment in Clinical Development*. J. Lippert, M. Brosch, O. von Kampen, M. Meyer, H.-U. Siegmund, C. Schafmayer, T. Becker, B. Laffert, L. Görlitz, S. Schreiber, P. J. Neuvonen, M. Niemi, J. Hampe and L. Kuepfer. CPT: Pharmacometrics & Systems Pharmacology, 1 (13), 1-8, 2012.
[10] *A computational systems biology software platform for multiscale modelling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks*. T.Eissing, L. Kuepfer, C. Becker, M. Block, K. Coboeken, T. Gaub, L. Goerlitz, J. Jaeger, R. Loosen, B. Ludewig, M. Meyer, C. Niederalt, M. Sevestre, H.-U. Siegmund, J. Solodenko, K. Thelen, U. Telle, W. Weiss, T. Wendl, S. Willmann and J. Lippert. Frontiers in Physiology, 2 (4), 1-10, 2011.
[11] www.systems-biology.com/products/pk-sim.html
[12] www.gnu.org/software/mcsim/
[13] www.mathworks.com/products/matlab/
[14] www.insilico-biotechnology.com/en/products/insilico-software#1
[15] *COPASI – a COmplexPAthway Simulator*. S. Hoops, S. Sahle, R. Gauges, C. Lee, J. Pahle, N. Simus, M. Singhal, L. Xu, P. Mendes and U. Kummer.Bioinformatics, 22, 3067-3074, 2006.
[16] *The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models*. M. Hucka, A. Finney, H. M. Sauro, H. Bolouri, J. C. Doyle, H. Kitano and the rest of the SBML forum. Bioinformatics, 19, 524-531, 2003.
[17] computox.colostate.edu/index.html

II-39: *Jason Cawley* Competitive brain and body growth model

Jason Cawley, Filippo Visco-Comandini, et al
Wolfram Research; Predator-Prey Team - representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community.

Background: Malnutrition has a considerable effect on the body development during childhood and, in particular, it affects brain development and cognitive abilities. In case of undernutrition, there is a competition for limited energy resources in the rapidly growing and maturing body, between the development of the brain and the development of the rest of the body.

Methods: We propose a mathematical model that links the daily nutrient intakes to brain and body development. The model characterizes normative infant growth curves and is able to simulate different scenarios like regular feeding, catch-up growth and ender- and over-nutrition based on changes in nutritional intake. Available energy generated from varied nutrient intake are assigned to different reservoirs (brain maintenance and its development, body maintenance and its development and physical activity). In case of underfeeding and malnutrition, these reservoirs will compete for the caloric resources.

Results: We first successfully characterized the normative growth curves associated with each percentile "growth channel" of the WHO standard growth curves. We subsequently used the model to estimate the daily nutrient intakes for the first 5 years of a longitudinal Guatemala study (N =92).

Discussion: The proposed brain and body predation growth model provides a framework for mechanistic exploration of anthropometric outcome and permits evaluations of different scenarios driven by nutrient intakes, such as regular feeding, malnutrition, and required caloric intake to support catch-up growth.

Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative

II-40: *Pascal Chanu* A model to predict progression free survival in patients with previously untreated HER2-positive progressive or recurrent locally advanced or metastatic breast cancer based on tumor growth inhibition metrics

Pascal Chanu (1), Laurent Claret (1), Rene Bruno (1), Chunze Li (2), Priya Agarwal (2), Sandhya Girish (2), Angelica Quartino (2), Jin Yan Jin (2), Dan Lu (2)
(1) Certara Strategic Consulting, France, (2) Clinical Pharmacology, Genentech

Objectives: To assess the link between tumor growth inhibition metrics (TGI) and progression free survival (PFS) based on previously untreated HER2-positive progressive or recurrent locally advanced or metastatic breast cancer (BC) data from the MARIANNE study [1].

Methods: TGI data from 868 patients who received trastuzumab emtansine (T-DM1), T-DM1 plus pertuzumab or trastuzumab plus a taxane in the Phase III study Marianne [1] were fit using tumor growth inhibition models [2, 3] by NONMEM version 7.3.0 [4]. The relationship between model-based estimates of TGI metrics [5]: growth rate (KG) estimated with the bi-exponential TGI model [2], early tumor shrinkage at week 8 (ETS) and time to growth (TTG) estimated with the simplified TGI model [3], as well as baseline covariates (~35) and PFS were tested in a multivariate parametric distribution survival model to select the best predictors of PFS in R version 3.1.2. Different distributions were tested. PFS model performance was evaluated by comparing the simulated distributions of PFS by quartile of TGI metrics or other significant covariates with the observed distributions in the MARIANNE study.

Results: The simplified TGI model [3] provided a better fit of the tumor size data compared to the bi-exponential TGI model [2]. Log(KG) estimated from the bi-exponential TGI model was identified as a much better predictor of PFS than TTG or ETS (based on difference in log-likelihood to the null model in a Cox univariate analysis). PFS (month) was best described by a lognormal distribution with a linear log(KG)-PFS link, and LDH, SGOT levels and the number of disease sites at baseline identified as statistically significant prognostic factors:

	Estimate	**Std. Error**	**P Wald test**
(Intercept)	-1.18	0.19	8.99e-10
logKG	-0.799	0.033	4.65e-127
LDH (U/L)	-0.000481	0.000119	5.37e-05
>2 disease sites	-0.216	0.074	0.00343
SGOT (U/L)	-0.00459	0.00151	0.00245
Log(standard deviation)	-0.193	0.030	1.63e-10

The model was qualified to predict PFS distribution by Log(KG) quartiles as well as by levels of the prognostic factors:

Median PFS (months)			
Log(KG) quartiles	**Observed**	**Predicted**	**95% PI**

Q1	not reached	35.0	27.7	45.1
Q2	14.6	16.4	13.7	19.6
Q3	10.4	10.9	9.2	13.0
Q4	5.3	4.9	4.1	5.8

Conclusions: A survival model that uses a model-based estimate of tumor growth rate to predict the PFS for previously untreated HER2-positive BC has been developed. This model can be used to support early decision making of investigational agents in development for this indication based on the TGI metrics.

References:

[1] Ellis PA, Barrios CH, Eiermann W et al. Phase III, randomized study of trastuzumab emtansine ± pertuzumab vs trastuzumab + taxane for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. J Clin Oncol (2015) 33 (suppl; abstr 507).
[2] Stein WD, Gulley JL, Schlom J, et al: Tumor regression and growth rates determined in ?ve intramural NCI prostate cancer trials: The growth rate constant as an indicator of therapeutic ef?cacy. Clin Cancer Res (2010) 17: 907-917.
[3] Claret L, Gupta M, Han K, et al. Evaluation of tumor size response metrics to predict overall survival in western and Chinese patients with first line metastatic colorectal cancer. J Clin Oncol (2013) 31: 2110-2114.
[4] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.
[5] Bruno R, Mercier F, Claret L. Evaluation of tumor-size response metrics to predict survival in oncology clinical trials. Clin Pharmacol Ther (2014) 95: 386-393.

II-41: *Aziz Chaouch* Building up a posteriori percentiles for Therapeutic Drug Concentration Monitoring

Aziz Chaouch (1,2), Robert Hooper (3), Chantal Csajka (1,4), Valentin Rousson (2), Yann Thoma (3), Thierry Buclin (1)

(1) Division of Clinical Pharmacology, University Hospital, Lausanne, Switzerland (2) Division of Biostatistics, Institute for Social and Preventive Medicine, University Hospital, Lausanne, Switzerland (3) School of Engineering and Business of the Canton of Vaud, Yverdon, Switzerland (4) School of Pharmaceutical Sciences, Universities of Geneva and Lausanne, Switzerland

Objectives: We propose to calculate a posteriori percentile curves (i.e. percentiles from the posterior predictive distribution of concentrations) for the rendering of Therapeutic Drug Concentration Monitoring results in a patient, for whom past concentration measurements are already available. We illustrate the clinical usefulness of such a posteriori percentiles to:
- Determine the probability that future concentrations lie within a prespecified therapeutic range, under either the current or a modified dosing regimen
- Detect significant changes in drug disposition, e.g. following drug-drug interactions or malfunction of elimination organs
- Identify patient adherence issues

Methods: Considering the population pharmacokinetic model of Voriconazole [1], a set of 1 to 10 simulated trough concentration measurements was generated for a fictive patient receiving 400 mg orally b.i.d., while assuming steady-state. The joint posterior distribution of random effects for this specific patient was obtained using the Sampling Importance Resampling (SIR) algorithm [2,3], while considering the parameter estimates of the model as known. Monte-Carlo simulations were then used to reconstruct the posterior predictive distribution of concentrations over the next dosing interval. This enabled us to assess the expectedness of future concentration measurements in the patient, and the probability of the next trough concentration to lie within the therapeutic range, under different dosing regimens.

Results: We show how the incremental consideration of historical information can reduce the width of the prediction interval for future concentrations in the patient being monitored. We also illustrate how a posteriori percentile curves may detect a future abnormal concentration measurement as the patient gradually becomes his/her own reference, whereas a priori percentiles fail to detect such abnormalities.

Conclusions: When past concentration measurements are available for a patient under monitoring, the rendering of a posteriori percentile curves depicts the likelihood of future concentrations in this patient, under the current or an adapted dosing regimen. Such percentiles constitute an important piece of information that can be graphically communicated to the attending physician, who can then judge whether a measured concentration is both expected and appropriate for his/her patient. This will contribute to better informed treatment decisions, representing a further step towards individualized drug dosage adaptation.

References:
[1] Pascual, A. et al. (2012) Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis, 55(3):381-390
[2] Rubin, D.B. (1988) Using the SIR algorithm to simulate posterior distributions. In Bayesian Statistics 3,

eds, M. H. Bernardo, K. M. DeGroot, D. V. Lindley, and A. F. M. Smith, Cambridge, MA: Oxford University Press, 395-402
[3] Smith, A.F.M. and Gelfand, A.E. (1992) Bayesian statitics without tears: A sampling resampling perspective. The American Statistician, 46(2):84-88

II-42: *Jonathan Chard* Pharmacometrics workflow: standards for provenance capture and workflow definition

Jonathan Chard (1), Justin Wilkins (2), Amy Cheung (3), Evan Wang (4), Mike K Smith (5), Phylinda Chan (5), Gareth Smith (6), Richard Kaye (1), Maria Luisa Sardu (7), Stuart Moodie (8)
(1) Mango Solutions, (2) Occams, (3) Astra Zeneca, (4) Eli Lilly, (5) Pfizer, (6) Cyprotex, (7) Merck Serono, (8) Eight Pillars Ltd

Objectives: To develop a standard, implemented with a workflow software tool, for capturing the full range of activities and entities that are performed during a pharmacometric analysis, based on existing standards. Capturing the provenance of task outputs (how was this created) as well as providing knowledge management for the pharmacometrics workflow (how did we get to this model) facilitates reproducibility, sharing, and communication of results with others. Using this standard, we can visualise the steps taken during the analysis, reproduce analysis steps, and capture decisions, assumptions, key steps, and support the process of quality control, as suggested in the definition of Model-Informed Drug Discovery and Development (MID3)[1]

Methods: Several existing workflow tools and provenance capture standards were evaluated [3,4,5], but the PROV-O ontology[2] was selected due to its wide adoption, extensibility and suitability for capturing the provenance and relationships between activities and entities within and across projects. Analysis artefacts, actions, information and relationships were mapped onto concepts defined within PROV-O. Tools were developed to support the pharmacometric workflow; storing files in Git [6], generating the provenance information representing the steps taken by the pharmacometrician, and to query the captured information to visualise, report, and regenerate the artefacts within an analysis.

Results: The standard allows tracking of users, software tools, and files in an analysis, while capturing assumptions, decisions and relationships extending beyond input to output. Information can be captured at multiple levels of detail, allowing a reviewer to understand key decisions taken during an analysis, or to trace through the software used to generate results. It is possible to identify project artefacts that are out of date (e.g. a diagnostic plot that should be recreated due to dataset change), and re-run activities. Analysts can apply this information to generate documentation, from run records to complete reports. Knowledge shared between team members is enhanced, avoiding duplication of work, increasing quality and reproducibility. Traceability assists reviewers and regulators to evaluate assumptions, results and conclusions.

Conclusions: Capturing structured information with software tools helps to ensure data integrity, facilitating QC and adoption of MID3 concepts.

Acknowledgements: This work is presented on behalf of the DDMoRe project (www.ddmore.eu).

References:
[1] EFPIA MID3 Workgroup. Good Practices in Model-Informed Drug Discovery and Development (MID3): Practice, Application and Documentation. CPT: Pharmacometrics Syst. Pharmacol. 2016 doi: 10.1002/psp4.12049
[2] PROV-O: The PROV Ontology. Timothy Lebo, Satya Sahoo, Deborah McGuinness, https://www.w3.org/TR/prov-o/
[3] Paolo Missier, Saumen Dey, Khalid Belhajjame, Victor Cuevas-Vicenttin, Bertram Ludascher. D-PROV:

Extending the PROV Provenance Model with Workflow Structure.
https://www.usenix.org/system/files/conference/tapp13/tapp13-final3.pdf
[4] Khalid Belhajjame , Oscar Corcho , Daniel Garijo , Jun Zhao , Paolo Missier , David Newman , Raul Palma , Sean Bechhofer , Esteban Garcia Cuesta , Jose Manuel Gomez-Perez , Graham Klyne , Kevin Page , Marco Roos , Jose Enrique Ruiz , Stian Soiland-Reyes , Lourdes Verdes-Montenegro , David De Roure , Carole A. Goble. Workflow-Centric Research Objects: First Class Citizens in Scholarly Discourse.
http://users.ox.ac.uk/~oerc0033/preprints/sepublica2012.pdf
[5] Khalid Belhajjame, Jun Zhao, Daniel Garijo, Matthew Gamble, Kristina Hettne, Raul Palma, Eleni Mina, Oscar Corcho, José Manuel Gómez-Pérez, Sean Bechhofer, Graham Klyne, Carole Goble : Using a suite of ontologies for preserving workflow-centric research objects.
http://www.sciencedirect.com/science/article/pii/S1570826815000049
[6] Git Distributed Version Control System. https://git-scm.com/

II-43: *Christophe Chassagnole* Modelling the Emergence of Resistance to Chemotherapeutics with Virtual Tumour

Frances Brightman, Eric Fernandez, David Orrell, Christophe Chassagnole
Physiomics plc

Objectives: Drug resistance is a major cause of treatment failure in cancer, and understanding and overcoming mechanisms of resistance is a key challenge in advancing cancer therapy[1]. Although the progression from cytotoxic chemotherapy to drugs aimed at specific molecular targets has improved response rates and reduced adverse effects, in the majority of cases there is still no effective treatment for metastatic disease[2]. Resistance arises from mutations in the genome of cancer cells and/or epigenetic changes[3]. The problem is compounded by considerable intra- and inter-tumour genetic heterogeneity, dictated by the genetic background and history of each cancer cell[2,3]. It is therefore becoming increasingly clear that cancer should be managed through personalized medicine[4], although this is unlikely to be widespread in clinical practice in the immediate future. In the interim, recent studies have shown that the emergence of drug-resistant disease can at least be delayed through treatment with novel dosing regimens[5,6].

Methods: Physiomics has developed a 'Virtual Tumour' (VT) technology that can predict how a tumour will respond to drug exposure. The VT technology integrates pharmacokinetic and pharmacodynamic effects, and models the way individual cells behave within a tumour population. These agent-based methods are particularly suitable for modelling multiple cell populations, and representing the heterogeneity of a clinical tumour. Given the significance of cancer drug resistance, and the form that future cancer therapy is likely to take, Physiomics is actively engaged in developing personalized medicine solutions. As a first step, we have incorporated chemotherapeutic resistance into our VT platform.

Results: The VT has been extended by the addition of a resistance module, which has been developed, calibrated and qualified using data taken from the literature[6]. This module captures the fundamental mechanism by which resistance arises. Through a case study also derived from the literature, we demonstrate that the extended VT can be applied to model the emergence of resistance in patient-derived xenografts. Furthermore, we show that the VT can be used to identify and optimize therapeutic strategies for delaying the emergence of drug resistance.

Conclusions: Our enhanced VT capability represents the first step towards a ground-breaking tool for developing personalized treatment, which is set to revolutionize cancer therapy in the near future, especially for patients with resistant disease.

References:

[1] Farrell, A. A close look at cancer. Nat. Med. 17, 262–265 (2011).
[2] Gottesman, M. M. Mechanisms of Cancer Drug Resistance. Annu. Rev. Med. 53, 615–627 (2002).
[3] Rebucci, M. & Michiels, C. Molecular aspects of cancer cell resistance to chemotherapy. Biochem. Pharmacol. 85, 1219–1226 (2013).
[4] Gonzalez de Castro, D., Clarke, P. A., Al-Lazikani, B. & Workman, P. Personalized Cancer Medicine: Molecular Diagnostics, Predictive biomarkers, and Drug Resistance. Clin. Pharmacol. Ther. 93, 252–259 (2013).
[5] Chmielecki, J. et al. Optimization of Dosing for EGFR-Mutant Non-Small Cell Lung Cancer with Evolutionary Cancer Modeling. Sci. Transl. Med. 3, 90ra59 (2011).

[6] Das Thakur, M. et al. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. Nature 494, 251–255 (2013).

II-44: *Chunli Chen* Assessment of Pharmacodynamic Interactions in the Mycobacteria Tuberculosis Infected Mouse using The Multistate Tuberculosis Pharmacometric Model and the General Pharmacodynamic Interaction Model

Chunli Chen (1), Sebastian G. Wicha (1), Gerjo J. de Knegt (2), Jurriaan E.M. de Steenwinkel (2), Ulrika SH Simonsson (1)

(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) Erasmus MC, Department of Medical Microbiology and Infectious Disease, University Medical Centre Rotterdam, Rotterdam, The Netherlands

Objectives: The aim of this work was to investigate pharmacodynamic (PD) interactions between the standard treatment drugs of sensitive *Mycobacterium tuberculosis* in an chronic mouse model using the Multistate Tuberculosis Pharmacometric (MTP) model [1] and the general pharmacodynamic interaction (GPDI) model based on the Bliss Independence criterion [2].

Methods: Pharmacokinetic (PK) models for rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) were developed using sparse PK data from separate infected BALB/c mice, combined with rich PK data from healthy BALB/c mice [3]. Infected BALB/c mice randomized to monotherapy received either 4 weeks of RIF (5, 10 or 20 mg/kg) or INH (12.5, 25 or 50 mg/kg) or EMB (50, 100 or 200 mg/kg) or PZA (75, 150 or 300 mg/kg). The PD biomarker colony forming unit (CFU) was measured after 1, 2 and 4 weeks treatment using 9 mice at each occasion. For the different duo, triple or quatro combinations of the drugs, fixed doses of 10 mg/kg RIF, 25 mg/kg INH, 100 mg/kg EMB and 150 mg/kg PZA were used and CFU was measured after 1, 2, 4, 8, 12 and 24-weeks of treatment using 3 mice at each occasion. Natural growth data was collected at 1, 3, 7, 14 and 21 days after infection. All modeling was done using NONMEM® 7.3[4] together with Perl-speaks-NONMEM [5], Xpose [5] and Pirana [6].

Results: In monotherapy, RIF was found to kill all three sub-states i.e. fast-multiplying (F), slow-multiplying (S) and non-multiplying bacteria (N) as well as to inhibit the growth rate of the F sub-state. INH had no effect on N, but killed F and S bacteria. Monotherapy of EMB and PZA displayed no detectable killing effects, because of lack of longitudinal PD data. Yet, in the presence of PZA, INH killed N bacteria. Antagonism was quantified between RIF and INH against S and N bacteria. This interaction increased log10 CFU/ml by approximately 0.79 and 0.86 compared with expected additivity on day 28 after treatment. EMB, itself inactive, synergized killing of RIF against N bacteria, which decreased log10 CFU/mL by 2.84 compared to expected additivity.

Conclusions: The present study results suggest that the proposed MTP model together with the GPDI model can be applied to both mono and combination therapy CFU data originating from animal studies. This approach provides a quantitative evaluation framework of potential PD interactions among anti-tuberculosis drugs in TB drug development.

References:

[1] Clewe O, Aulin L, Hu Y, et al. (2015) A multistate tuberculosis pharmacometric model: a framework for studying anti-tubercular drug effects in vitro. J Antimicrob Chemother: 1460-2091

[2] Wicha SG, Chen C, Clewe O, Simonsson US. (2016) A general pharmacodymamic interaction model based on the Bliss Independence criterion. PAGE abstract, Lisbon

[3] de Steenwinkel JEM, Aarnoutse RE, de Knegt GJ, et al. (2013) Optimization of the rifampin dosage to improve the therapeutic efficacy in tuberculosis treatment using a murine model. Am J Respir Crit Care

Med 187:1127–1134
[4]Beal S, Sheiner LB, Boeckmann A, Bauer RJ. (2009) NONMEM User's Guides (1989-2009), Icon Development Solutions, Ellicott City, MD, USA
[5]Keizer RJ, Karlsson MO, Hooker A. (2013) Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacomet Syst Pharmacol 2:e50
[6]Keizer RJ, van Benten M, Beijnen JH, et al. (2011) Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed 101:72–79

II-45: *Charles Chen* Comparison of Recursive Partitioning Analysis and Receiver Operating Characteristic (ROC) Analysis for Patient Identification

Shang-Chiung Chen, Matthew Riggs, Eveline Nueesch, Alexander Strasak, Jonathan French, Jin Jin, Sandhya Girish, Chunze Li
Genentech, Inc.

Objectives: Exposure–response (E-R) analyses have become an integral part in oncology drug development and have played a critical role in identifying patients with low exposure who might benefit from an alternative dose and/or regimen. Therefore, reliably and consistently identifying these patients is important to allow evaluation of alternative dose and/or regimen in these patients. The objective of this analysis is to compare two methodologies using a case study, namely recursive partitioning analysis and receiver operating characteristic (ROC) analysis, to identify the key baseline predictors of patients with low exposure

Methods: Methodologies for patient identification were exemplified using data from an oncology Phase 3 trial. All data exploration and analyses were conducted using version 3.2.1 of R. For recursive partitioning analysis, two packages (rpart and party) were used and different analysis-level variables were explored, including minimum bin sizes (range: 15–40) and the inclusion/exclusion of missing dependent variable values. Prediction of low exposure patients by baseline characteristics was also evaluated using receiver operating characteristics (ROC) analysis and the corresponding area under curve (AUC)

Results: Results from two recursive partitioning packages were typically similar, with shed antigen, tumor burden, SGOT, and albumin as the most prevalent baseline patient characteristics chosen. Across various analysis-level variables evaluated for recursive partitioning analysis, only one level of split can be reached except for small minimum bin sizes, and the cut-offs of the baseline patient characteristics for the splits are comparable. The resulting patient identification criteria, in general, had low (range 23.5 - 44%) sensitivity and relatively high (range 81.3 – 97.9%) specificity. Visualized by ROC curve and corresponding AUC, the baseline patient characteristics predictive of low exposure were consistent to those identified by recursive partitioning.

Conclusions: Two methodologies commonly used for patient identification resulted in similar set of baseline patient characteristics predictive of low exposure. While recursive partitioning analysis can provide initial cut-offs of baseline characteristics for patient identification, the cut-offs may be further refined based on ROC curve for logistical purpose. Reliability to identify low exposure patients in an external population remains to be evaluated.

II-46: *Maxwell Tawanda Chirehwa* Semi-mechanistic pharmacokinetic model for Isoniazid and Acetyl isoniazid in a cohort of TB/HIV co-infected patients

Maxwell T. Chirehwa (1), Helen McIlleron (1), Lubbe Wiesner (1), Dissou Affolabi (2), Oumou Bah Sow (3), Andrzej Bienczak (1), Corinne Merle (4) and Paolo Denti (1) on behalf of RAFATB-net
(1)Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa; (2)National TB programme, Benin; (3)Service de Pneumopthysiologie, Hopital Ignace Deen, Conakry, Guinea; (4)London School of Hygiene & Tropical Medicine (London, UK)

Objective: Isoniazid (INH) metabolism primarily involves acetylation by N-acetyltransferase-2 (NAT2) to AcINH, and the genes encoding NAT2 are highly polymorphic, causing differential expression among populations (1-3). Our objective is to describe pharmacokinetics (PK) of isoniazid (INH) and acetyl-isoniazid (AcINH) among TB/HIV co-infected patients.

Methods: Blood samples were collected from 150 TB/HIV co-infected patients from West Africa just before and at 2, 3, 6, and 10 hours after dose administration, at steady-state. Dosing was weight-adjusted according to WHO guidelines (4). NONMEM 7.3 was used to analyse PK data. Allometric scaling was employed to account for differences in body size.

Results: INH PK was best described by using a two-compartment disposition model and a well-stirred liver model accounting for first-pass metabolism. Hepatic volume of distribution and plasma flow (Q_H) were fixed to 1 L and 50 L/h and allometrically scaled, while INH unbound fraction was fixed to 95% (5). A mixture model with 2 approximately equal subpopulations was applied to intrinsic CL to describe the effect of NAT2 polymorphisms. Intrinsic CL for fast acetylators was around 5-fold that of slow acetylators, resulting in an E_H of 0.39 for fast acetylators and 0.12 for slow. An additional clearance from central compartment was identified and estimated to be 8 L/h. AcINH was the product of the hepatic acetylation and was described using a two-compartment model and CL estimated to be 17 L/h.
Allometric scaling using FFM on all clearance and volume parameters was supported by the data. Between-subject variability was included for k_a, and CL and volume of both INH and AcINH. Between-occasion variability was included on pre-hepatic bioavailability.

Conclusions: The proposed model was able to separate acetylation (responsible for formation of AcINH) from other elimination pathways, and it quantified the difference between fast and slow acetylators. The estimated values are consistent with previous literature reports (6,7). Similar to recent population PK models for antituberculosis treatment (3,8-9), FFM was found to be a better descriptor of body size than total weight for allometric scaling. This suggests that body composition should be taken into account when optimising the dosing strategy for antituberculosis drugs.

Funding: This project is funded by The European & Developing Countries Clinical Trials Partnership (EDCTP).

References

[1] Ellard GA, Gammon PT. 1976. Pharmacokinetics of isoniazid metabolism in man. J. Pharmacokinet. Biopharm. 4:83–113.
[2] Parkin DP, Vandenplas S, Botha FJ, Vandenplas ML, Seifart HI, van Helden PD, van der Walt BJ, Donald PR, van Jaarsveld PP. 1997. Trimodality of isoniazid elimination: phenotype and genotype in patients with tuberculosis. Am J Respir Crit Care Med, 1997/05/01 ed. 155:1717–1722.
[3] Denti P, Rustomjee R, Mthiyane T, Onyebujoh P, Smith P, Mcilleron H. 2011. Population

pharmacokinetics of Isoniazid in South African TB patientsThe 4th international workshop on clinical pharmacology of TB drugs. Chicago, IL.
[4] World Health Organization. 2003. Treatment of tuberculosis: Guidelines for national programmes (3rd edition). WHO/CDS/TB/2003.313. Gevena, Switzerland.
[5] Alffenaar J-WC, Uges DRA, Greijdanus B, Kok WT, Jongedijk EM, Lijke H van der, Sturkenboom MGG. 2015. Quantification of isoniazid, pyrazinamide and ethambutol in serum using liquid chromatography-tandem mass spectrometry. J. Appl. Bioanal. 1:89–98.
[6] Weber WW, Hein DW. 1979. Clinical Pharmacokinetics of Isoniazid. Clin. Pharmacokinet. 4:401–422.
[7] Ramachandran G, Hemanth Kumar AK, Sarala K, Padmapriyadarsini C, Anitha S, Tharani CB, Kumaraswami V, Swaminathan S. 2007. Urine levels of rifampicin & isoniazid in asymptomatic HIV-positive individuals. Indian J. Med. Res. 125:763.
[8] Chirehwa MT, Rustomjee R, Mthiyane T, Onyebujoh P, Smith P, McIlleron H, Denti P. 2016. Model-Based Evaluation of Higher Doses of Rifampin Using a Semimechanistic Model Incorporating Autoinduction and Saturation of Hepatic Extraction. Antimicrob. Agents Chemother. 60:487–94.
[9] Denti P, Jeremiah K, Chigutsa E, Faurholt-Jepsen D, PrayGod G, Range N, Castel S, Wiesner L, Hagen CM, Christiansen M, Changalucha J, McIlleron H, Friis H, Andersen AB. 2015. Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Newly Diagnosed Pulmonary TB Patients in Tanzania. PLoS One 10:e0141002

II-47: *Hyewon Chung* Population pharmacokinetics of F-ara-A after fludarabine administration in pediatric hematopoietic stem cell transplantation patients

Hyewon Chung (1), Su-jin Rhee (1), Kyung Taek Hong (2), Hyoung Jin Kang (2), In-Jin Jang (1), Kyung-Sang Yu (1)

(1) Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, (2) Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Objectives: Fludarabine, a prodrug that is dephosphorylated to F-ara-A [1], is used as a component of conditioning regimens of hematopoietic stem cell transplantation (HSCT). However, the pharmacokinetic (PK) data of F-ara-A in pediatric patients is limited. The objective of this study was to develop a population PK model of F-ara-A after fludarabine administration in pediatric patients.

Methods: A total of 802 samples obtained from 43 pediatric patients were included for population PK analysis. Among them, 40 patients received fludarabine 40mg/m^2 as a 30 minute infusion once daily for 6 days. The analysis was performed using non-linear mixed-effects modelling as implemented in NONMEM version 7.3. Covariates including body surface area (BSA), weight, age, serum creatinine, and sex were evaluated and the final model was selected based on decrease in objective function, diagnostic plots, and visual predictive check.

Results: A two-compartmental model with proportional residual error adequately described the PK of F-ara-A. BSA was a significant covariate for clearance (CL), central volume of distribution (V2), and peripheral volume of distribution (V2) using a power function. The typical population estimates of CL, V1, and V2 for a subject with BSA of 1.254 m^2 were 10.4 L/h, 36.8 L, and 43.2 L, respectively. The inter-individual variability were described for CL (30.7%), V1 (23.9%), V2 (25.6%), and inter-compartmental clearance (35.7%).

Conclusions: Population PK parameters for F-ara-A were successfully estimated in paediatric patients. This model can be used to guide fludarabine therapy, and to evaluate relationships between PK and clinical outcome.

References:

[1] Gandhi, V, Plunkett, W. Cellular and clinical pharmacology of fludarabine. Clin Pharmacokinet (2002) 41(2):93-103.

II-48: *Laurent Claret* A model to predict progression-free survival in patients with renal cell carcinoma based on week 8 change in tumor size

Laurent Claret (1), Jenny Zheng (2), Francois Mercier (1), Pascal Chanu (1), Ying Chen (3), Brad Rosbrook (4), Pithavala, Yazdi (3), Peter A. Milligan (2), Rene Bruno (1)
(1) Pharsight Consulting Services, Pharsight, a CertaraTM Company, France, (2) Pfizer Pharmacometrics, Global Clinical Pharmacology, USA and UK, (3) Pfizer Clinical Pharmacology, La Jolla, CA, USA, (4) Pfizer Statistics, La Jolla, CA, USA

Objectives: To assess the link between early tumor shrinkage (ETS) and progression-free survival (PFS) based on historical first-line metastatic renal cell carcinoma (mRCC) data.

Methods: Tumor size data from 921 patients with first-line mRCC who received interferon-alpha, sunitinib, sorafenib or axitinib in 2 Phase III studies [1, 2] were fit using a simplified tumor growth inhibition model [3]. The relationship between model-based estimates of ETS at week 8 [4], as well as the baseline prognostic factors and PFS were tested in a multivariate log-logistic distribution model. Both models were implemented in NONMEM version 7.3.0 [5]. PFS model performance was evaluated by comparing the simulated distributions of PFS and treatment hazard ratio (HR) with the observed PFS and HR in the two studies. In addition, an external validation was conducted using data from an independent Phase II mRCC study [6]. The relationship between the differences in ETS and expected HR of an investigational treatment vs. sunitinib was simulated.

Results: A model with a non-linear ETS-PFS link, using albumin level and presence of bone metastases at baseline as prognostic factors, was qualified to predict PFS distribution by ETS quantiles. Additionally, the model was used to predict the HRs of sunitinib vs. interferon-alpha and axitinib vs. sorafenib. For sunitinib vs. interferon alfa, the median predicted HR was 0.58 with a 95% prediction interval (PI) of 0.49-0.69 compared to the observed HR of 0.54 [1]). The model was also qualified in simulating PFS distribution and HR in the independent study [6]. The simulations suggest that if a new investigational treatment could further reduce ETS at week 8 by 30% compared with sunitinib, an expected HR [95% PI] of the new treatment vs. sunitinib would be 0.59 [0.46,0.79].

Conclusions: A model that uses early change in tumor size to predict the HR for PFS between treatments for first-line mRCC has been developed. Such a model can be used to support early decisions for investigational agents in development for this indication.

References:
[1] Motzer RJ, Hutson TE, Tomczak P et al (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115-124.
[2] Hutson TE, Lesovoy V, Al-Shukri S et al (2013). Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 14:1287-1294.
[3] Claret L, Gupta M, Han K, et al (2013) Evaluation of tumor size response metrics to predict overall survival in western and Chinese patients with first line metastatic colorectal cancer. J Clin Oncol 31:2110-2114.
[4] Bruno R, Mercier F, Claret L (2014) Evaluation of tumor-size response metrics to predict survival in oncology clinical trials. Clin Pharmacol Ther 95:386-393.
[5] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.

[6] Rini BI, Melichar B, Ueda T et al (2013). Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomized double-blind phase 2 trial. Lancet Oncol 14:1233-1242

II-49: *Yumi Cleary* Physiologically –based pharmacokinetic (PBPK) and population PK (PPK) modeling for basimglurant - assessment of predicted variability by the PBPK model and its utility

Yumi Cleary (1), Valerie Cosson (1), Stephen Fowler (1), Gerard Greig (1), Elena Guerini (1), Navita Mallalieu (2) and Neil Parrott (1)
(1) Roche Innovation Center Basel, Switzerland, (2) Roche Innovation Center, NYC, USA

Objectives: Basimglurant is a small molecule currently developed for major depressive disorder. It is eliminated by hepatic metabolism through CYP enzymes 1A2 and 3A4. Both PBPK and PPK models were developed. The ability of the PBPK model to predict between-subject variability was assessed by comparison to the variability estimated through the PPK model. Subsequently, utility of the PBPK model to assist in sample size calculations for a drug-drug interaction (DDI) study with ketoconazole was investigated.

Methods: A PBPK model was developed based on physicochemical properties, in vitro and clinical PK data using SimCYP version 12.1. A PPK model was developed based on 3762 basimglurant plasma concentrations obtained from 164 individuals using NONMEM (Version 7, level 1, double precision). Simulations for 0.5 mg basimglurant once daily for 14 days were performed with the PBPK and the PPK models for 1000 virtual individuals with exactly the same distributions of demographics. The median and 5^{th}-95^{th} percentiles of simulated basimglurant plasma concentration profiles as well as distributions of simulated C_{max} and AUCτ at steady state were compared between the models. Subsequently, a ketoconazole DDI trial with the number of subjects varying between 3 to 60 was simulated with 10 replications. The median and range of the median AUC ratios of basimglurant in the absence and presence of ketoconazole were examined in relation to the number of subjects in each trial.

Results: The median and 5^{th}-95^{th} percentiles of basimglurant plasma concentrations simulated with the PBPK model as well as the distributions of the predicted C_{max} and AUCτ showed good agreement with the PPK model (median C_{max} is 3.09 vs. 3.31 ng/mL, and median AUCτ is 40.6 ng*h/mL vs. 43.1 ng*h/mL between PBPK vs. PPK model simulations, respectively). The range of the median AUC ratios of basimglurant in trials with 3 to 10 subjects was larger and fluctuated more widely than in the trials with more than 10 subjects. Constant median and range of median AUC ratios were seen in trials with 14 to 60 individuals per trial indicating that a sample size of 14 would be sufficient to investigate the DDI with reasonable confidence.

Conclusions: The SimCYP predicted between-subject variability of basimglurant was in accordance with the estimates made with a PPK model and the utility of the PBPK model to determine an appropriate sample size for a DDI study with ketoconazole was shown.

II-50: *Oskar Clewe* Pre-clinical Susceptibility Characterization and Pharmacodynamic Interaction Assessment Using the Multistate Tuberculosis Pharmacometric Model

Oskar Clewe (1), Sebastian G. Wicha (1), Corné de Vogel (2), Jurriaan E. M. de Steenwinkel (2), Ulrika S. H. Simonsson (1)

(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, The Netherlands.

Objectives: For diseases such as tuberculosis, where a combination of drugs are needed to effectively combat the bacterial infestation, the possibility of both positive and negative pharmacodynamic drug interactions exist. From many perspectives establishing an initial optimal combination of drug concentrations is not reasonable to carry out in a clinical setting. This information could rather be provided from a pre-clinical setting in which cost and ethical implications are minor. This work aimed at characterizing the susceptibility of *Mycobacterium tuberculosis (M. tuberculosis)* to rifampicin (RIF), isoniazid (INH) and ethambutol (ETH) and assessing the pharmacodynamic interactions of combinations of the three drugs using *in vitro* time kill data.

Methods: *In vitro* time kill experiments were performed with *M. tuberculosis* genotype strain Beijing 1585 using both single and combination series of RIF, INH and ETH concentrations. Viability, defined as colony forming units (cfu), was assessed at day 1, 2, 3 and 6 after drug exposure. The Multistate Tuberculosis Pharmacometric (MTP) model framework [1] and the general pharmacodynamic interaction (GPDI) model based on the Bliss Independence criterion [2] was used to characterize the natural growth and drug effect from mono and combination exposure.

Results: A statistical antagonistic pharmacodynamic interaction was found between RIF and ISO with a larger antagonistic effect on ISO by RIF than vice versa. An antagonistic interaction was found between ISO and ETH, but the interaction effects were similar between the two drugs and the maximum fractional increase in EC_{50} of <1 was similar to that of the antagonistic interaction between ETH and RIF. In contrast, a statistical synergistic interaction was found between RIF and ETH and there was no significant difference in the size of synergy exerted by RIF on ETH and vice versa.

Conclusions: We have shown that the MTP model together with the newly developed GPDI model approach can be used to characterize the *in vitro* pharmacodynamic interactions of three first-line anti-tuberculosis drugs. As this type of interaction assessment allows for characterization of drug A´s interaction with B and drug B´s interaction with A, it is highly suitable as input to selection of phase 2b anti-tuberculosis combination regimens.

References:

[1] Clewe O, Aulin L, Hu Y, Coates AR, Simonsson USH. A multistate tuberculosis pharmacometric model: a framework for studying anti-tubercular drug effects in vitro. JAC 2015; Epub Dec 24 2015.
[2] Wicha SG, Chen C, Clewe O, Simonsson USH. A general pharmacodynamic interaction model based on the Bliss Independence criterion. Abstract. PAGE 2016. Lisbon.

Acknowledgments: The research was funded by the Swedish Research Council and the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement n°115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

II-51: *Pieter Colin* Propofol breath monitoring as a potential tool to improve the prediction of intraoperative plasma concentrations

Pieter Colin (1,2), Douglas J. Eleveld (1), Johannes P. van den Berg (1), Hugo E.M. Vereecke (1), Michel M.R.F. Struys (1,3), Gustav Schelling (5), Christian C. Apfel (4), Cyrill Hornuss (5)
(1) Department of Anesthesiology, University Medical Center Groningen, University of Groningen, The Netherlands; (2)Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium; (3) Department of Anesthesia, Ghent University, Gent, Belgium; (4) Department of Epidemiology and Biostatistics, University of California, San Francisco; (5) Department of Anaesthesiology, Klinikum der Universität München, Munich, Germany

Objectives: To develop an extension to the current state-of-the-art PK model for propofol [1] which allows the simultaneous description of propofol plasma and breath concentrations. To apply this model in a Bayesian forecasting setting to investigate whether breath monitoring of propofol could improve the predictive performance of the current PK model for intraoperative propofol plasma concentrations.

Methods: Propofol breath and plasma concentration measurements were obtained from twenty healthy volunteers who were dosed using a target-controlled infusion system (TCI) based on Schnider et al.[2]. The FOCE algorithm with interaction as implemented in NONMEM® (version 7.3; Icon Development Solutions, Hanover, MD, USA) was used to fit different breath models to our dataset. Afterwards, a simulation study was conducted in which cross-validation was used to compare the predictive performance of the final model when different amounts of breath data were used.

Results: The final model consisted of (i) an effect-site compartment to accommodate the delay between plasma and breath measurements, (ii) a scale parameter (K) to accommodate the unit conversion from µg/mL for the plasma measurements to parts per billion (ppb) for the measured breath concentrations and (iii) a linear time-dependent change in K over time. Goodness-of-fit plots and numerical performance metrics (median prediction error (MdPE) and root mean squared error) demonstrate that the developed model adequately describes exhaled propofol concentrations. When this model is used to predict propofol plasma concentrations from measured breath concentrations, the predictive performance is markedly better than the current state-of-the-art PK model. We found that the MdPE decreased from 42.8% when no breath concentrations were used to -1.05% when more than 35 minutes of breath concentrations were used.

Conclusions: We show that the current state-of-the-art pharmacokinetic model is easily extended to reliably describe propofol kinetics in exhaled breath. Furthermore, we show that the predictive performance of the *a-priori* model is improved by Bayesian adaptation based on the measured breath concentrations thereby allowing further treatment individualization and a more stringent control on the targeted plasma concentrations during general anesthesia.

References:
[1] Eleveld, D.J., Proost, J.H., Cortinez, L.I., Absalom, A.R. & Struys, M.M. A general purpose pharmacokinetic model for propofol. Anesthesia and analgesia 118, 1221-37 (2014)
[2] Schnider, T.W. *et al.* The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* **88**, 1170-82 (1998)

II-52: *Emmanuelle Comets* Operational characteristics of saemix, an R package implementing the SAEM algorithm

Emmanuelle Comets (1), Audrey Lavenu (2), Marc Lavielle (3)
(1) INSERM UMR1137 IAME, Paris, France; University Denis Diderot, Paris, France; (2) University Rennes-I, Rennes, France; INSERM CIC 1414, Rennes, France; (3) INRIA Saclay, Popix University Paris Sud, France

Objectives: The saemix package for R [1] provides an implementation of the SAEM (Stochastic Approximation Expectation Maximization) algorithm. In the present paper, we assess the operational characteristics of saemix in terms of performance and scalability, using simulated data.

Methods: The SAEM algorithm is used to obtain maximum likelihood estimates of the parameters of nonlinear mixed effects models without any linearisation of the model [2,3]. The SAEM algorithm uses an EM algorithm, where the unknown individual parameters are treated as missing data, and replaces the usual E-step with a stochastic approximation step [4,5]. The saemix package makes use of the S4 classes in R to provide a user-friendly functions for estimation, diagnostics and summary.
We applied saemix on simulated data from Plan et al., who created it to compare the performance of various software [6]. A sigmoid Emax model was fitted to dose-response data simulated with relatively large curvature (gamma=3), under a rich and a sparse design (respectively 4 and 2 points per subject). We compared the performance of saemix with results from nlme [7] and nlmer from lme4 [8].
In parallel, we investigated the scalability of the algorithm by showing runtimes across models with varying numbers of parameters and across different designs.

Results: In the rich design, saemix was able to provide unbiased estimates of the population parameters, while both nlme and nlmer had trouble estimating ED50 and its variability. In the sparse design, the three algorithms exhibited bias but saemix showed the best performance. nlmer and to a lesser extent nlme exhibited convergence issues, especially for the sparse design.
As expected due to the stochastic nature of the algorithm, runtimes for saemix increased as a function of the number of random effects in the model and of the number of subjects in the dataset. We also implemented an ODE model using the standard R solver (deSolve) but this proved extremely slow.

Conclusions: The saemix package provides the SAEM algorithm for R users, as an alternative to linearisation-based algorithms, implemented in nlme [7], or quadrature methods, implemented in glmmML or lme4 [8]. Current development focuses on extending the capabilities of the package via new models, such as ODE systems or hidden Markov models [9], extended diagnostics, and automating covariate handling.

References:
[1] R Development Core Team (2006). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
[2] Delyon B, Lavielle M, Moulines E (1999). Convergence of a stochastic approximation version of the EM algorithm. Annals of Statistics 27:94-128.
[3] Kuhn E, Lavielle M (2004). Coupling a stochastic approximation version of EM with a MCMC procedure. ESAIM P&S 8:115-31.
[4] Kuhn E, Lavielle M (2005). Maximum likelihood estimation in nonlinear mixed effects models. Comput Stat Data Anal 49:1020-38.
[5] Lavielle M (2014). Mixed Effects Models for the Population Approach - Models, Tasks, Methods and

Tools. Chapman & Hall/CRC Biostatistics Series, CRC Press, Boca Raton, Florida, USA
[6] Plan E, Maloney A, Mentré F, Karlsson M, Bertrand J (2012). Performance Comparison of Various Maximum Likelihood Nonlinear Mixed-Effects Estimation Methods for Dose-Response Models. AAPS J 14:420-32.
[7] Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core team (2009). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-96.
[8] Bates D, Maechler M (2010). lme4: Linear mixed-effects models using S4 classes. R package version 0.999375-34.
[9] Delattre M (2010). Inference in mixed Hidden Markov models and applications to medical studies. J Soc Franc Stat 151:90-105.

II-53: *Valerie Cosson* Amyloid related imaging abnormalities (ARIA): Time to event modeling to identify new Phase 3 doses and dosing regimens for Gantenerumab

Ronald Gieschke, Sylvie Retout, Nicolas Frey, Cornelia Weber, Jean Eric Charoin, Johann Laurent, Valérie Cosson, Daniel Serafin, Carsten Hofmann
Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: SCarlet RoAD (SR) was set up as a pivotal Phase 3 study to evaluate the effect of 105 and 225 mg subcutaneous every 4 weeks of anti-amyloid compound gantenerumab (GAN) in prodromal Alzheimer's disease. Following a futility analysis, dosing was stopped as there was no effect on AD scales at 2 years (N = 312). No new safety signals were observed, especially amyloid-related imaging abnormality-vascular edema (ARIA-E) events were manageable. At the same time, results from a Phase 1b study of aducanumab (ADU), a compound similar to GAN, became available [1]. ADU doses up to 10 mg/kg IV Q4W were explored and showed significant effects on AD scales, but also a large percentage of ARIA-E events in APOE e4 carriers. This suggested that higher doses of GAN may be of value to explore for clinical efficacy and safety. Here we carried out time to event analyses to describe the relationship between drug concentrations and cumulative occurrence of ARIA-E.

Methods: Relationships between drug concentrations and ARIA-E events were modeled with a hazard function first applied to anti-amyloid antibody bapineuzumab [2]. This function is dependent on study time (steadily decreasing the hazard to zero), drug serum concentrations, and APOE e4 carrier-status. Drug serum concentrations resulted from a population PK analysis of SR data. ARIA-E events were judged on MRI images taken every three month. An external validation of the model was performed with the Phase 1b ADU data. Using that model together with a biomarker (PET) model [3], new dose/dosing regimens matching pre-specified criteria of ARIA-E rate and brain amyloid plaque removal were investigated by simulation.

Results: Only hazard parameters related to drug concentrations, EC50 and Emax, were estimated. Other parameters, e.g. baseline hazard for e4 carriers, were fixed to values derived from [2]. Parameters could be estimated although with 83% relative standard error for EC50. Keeping all parameters fixed to estimated values, cumulative ARIA-E events were predicted and compared for the dosing regimens applied in the Phase 1b study of ADU. Graphical analysis revealed no noteworthy deviations. For each e4 carrier status, GAN titration regimens could be worked out balancing ARIA-E cumulative risk and effects on plaque removal (PET).

Conclusions: Quantitative clinical pharmacology analysis provided a model for ARIA-E events currently being used to define titration regimens in ongoing GAN studies.

References:
[1] Sevigny J et al, 67th Annual Meeting of the American Academy of Neurology, Washington DC, US (2015).
[2] Hutmacher M et al, 7th American Conference on Pharmacometrics, Fort Lauderdale, US (2013)
[3] Frey, N et al. Abstr PAGE 25, Lisbon, Portugal (2016)

II-54: *Sinziana Cristea* Maturation of Glomerular Filtration throughout the paediatric age-range; a comparison of different functions

Sînziana Cristea (1), Elke H.J. Krekels (1), Karel Allegaert (3,4), Amin Rostami-Hodjegan (5,6), Catherijne A.J. Knibbe (1,2)

(1) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands; (2) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands; (3) Intensive Care and Department of Pediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands; (4) Department of Development and Regeneration, KU Leuven, Belgium; (5) Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK; (6) Manchester Pharmacy School, Manchester University, Manchester,UK

Objectives: Glomerular filtration (GF) has a key role in the renal elimination of many drugs. Establishing an accurate ontogeny function for this route is necessary to guide paediatric dosing regimens of drugs eliminated through GF. Here, the performances of published functions describing the maturation of GF rate (GFR) [2-6] are compared to observed values in the paediatric population[1].

Methods: The published GFR functions were either based on compounds from which 'true' GFR was derived (i.e. Cr-EDTA, inulin, mannitol[2-4],[6]) or on clearance estimations of drugs mainly excreted by GFR (i.e. aminoglycosides[5]). These functions relied on a single demographic characteristic (i.e. bodyweight [2,5] or body surface area [3]) or on a combination of characteristics (i.e. bodyweight with postmenstrual age [4,6]) to describe the GFR maturation profile. A paediatric population of 3200 individuals between the ages of 2.5 weeks and 20 years was simulated using Simcyp v13. The obtained demographic characteristics were then used to predict GFR with the published functions. The comparison between GFR predictions [2-6] and observations [1] was performed at two levels: qualitatively, based on visual comparison of GFR predictions and quantitatively, based on % prediction error (PE%) with an acceptance range of ±50%.

Results: All the five published functions were found to describe similar maturation patterns, within an acceptable PE% range throughout the entire age-range (absolute PE%: 17%-36%). However, for all functions, there was a tendency towards underprediction of GFR below the age of 5 years. The closer the predictions were to the adult value, the higher the prediction accuracy. When compared to the observed data, the function by Hayton[2] had the lowest PE% whereas the function from De Cock[5] had the highest PE%. Rhodin[4] and Salem[6] had overall similar absolute PE% values (22.5% vs 24%) and also when stratified per age range (

Conclusions: The GFR maturation functions based on data from compounds that measure 'true' GFR have an overall better performance than the one based on drug clearance. All functions underpredict GFR below the age of one year.

References:

[1] M. I. Rubin, E. Bruck, M. Rapoport, M. Snively, H. McKay, and a Baumler, "Maturation of Renal Function in Childhood: Clearance Studies.," *J. Clin. Invest.*, vol. 28, no. 5 Pt 2, pp. 1144–62, 1949.
[2] W. L. Hayton, "Maturation and growth of renal function: dosing renally cleared drugs in children.," *AAPS PharmSci*, vol. 2, no. 1, p. E3, 2000.
[3] T. N. Johnson, A. Rostami-Hodjegan, and G. T. Tucker, "Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children," *Clin. Pharmacokinet.*, vol. 45, no. 9, pp. 931–956, 2006.

[4] M. M. Rhodin, B. J. Anderson, a. M. Peters, M. G. Coulthard, B. Wilkins, M. Cole, E. Chatelut, A. Grubb, G. J. Veal, M. J. Keir, and N. H. G. Holford, “Human renal function maturation: A quantitative description using weight and postmenstrual age,” *Pediatr. Nephrol.*, vol. 24, no. 1, pp. 67–76, 2009.
[5] R. F. W. De Cock, K. Allegaert, J. M. Brussee, C. M. T. Sherwin, H. Mulla, M. De Hoog, J. N. Van Den Anker, M. Danhof, and C. a J. Knibbe, “Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: Towards a semi-physiological function for maturation in glomerular filtration,” *Pharm. Res.*, vol. 31, no. 10, pp. 2643–2654, 2014.
[6] F. Salem, T. N. Johnson, K. Abduljalil, G. T. Tucker, and A. Rostami-Hodjegan, “A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on in vivo data,” *Clin. Pharmacokinet.*, vol. 53, no. 7, pp. 625–636, 2014.

II-55: *Damien Cronier* PK/PD Modeling of Overall and Progression-Free Survival in Advanced Soft Tissue Sarcoma Patients Treated With Olaratumab in Combination with Doxorubicin.

Gary Mo (1), Robin L. Jones (2), John R. Baldwin (1), Randy D. Nichols (1), Debra R. Luffer-Atlas (1), Robert L. Ilaria (1), Ilaria Conti (1), William D. Tap (3), Damien M. Cronier (4)
(1) Eli Lilly and Company, Indianapolis, USA, (2) Fred Hutchinson Cancer Research Center, Seattle, USA, Memorial Sloan Kettering Cancer Center, New York City, USA (3) Eli Lilly and Company, Windlesham, UK (4)

Objectives: Olaratumab (Olara), a recombinant human IgG1 monoclonal antibody, is a PGDFRα antagonist. Olara plus doxorubicin (Dox) improved survival vs Dox in an open-label, randomized Phase 2 soft tissue sarcoma (STS) trial (NCT01185964) [1]. We characterized the exposure-response relationship of Olara for progression free survival (PFS) and overall survival (OS).

Methods: Patients received Dox (75 mg/m2 Day 1) with (Arm A) or without (Arm B) Olara (15 mg/kg Days 1 and 8) for up to eight 21-day cycles. In Arm A, Olara monotherapy continued after Dox until disease progression, and Arm B patients could receive Olara after progressing with Dox. Data from patients in both Arm A (n=67) and Arm B (n=66) were used to develop the PFS and OS time-to-event models. Various hazard models were evaluated (exponential, Weibull, Gompertz, combined Weibull/Gompertz). The effect of Olara was explored using the average Olara serum concentration (Cavg) and trough Olara serum concentration in cycle 1 (Cmin1), both simulated using individual patient post-hoc PK parameters estimated by PopPK modelling. Additional covariates were evaluated for potential effects on PFS/OS.

Results: OS and PFS were both best described by survival models with an exponential hazard function. The effect of Olara on PFS/OS was captured by an inhibitory Emax function with Hill coefficient, regardless of the PK endpoint (Cavg or Cmin1) considered. The Olara EC50s for PFS (ECmin150 = 82 μg/mL, ECavg50 = 179 μg/mL) and those for OS (ECmin150 = 66.1 μg/mL, ECavg50 = 134 μg/mL) corresponded to the median and 25th percentile of Cmin1/Cavg in the study, respectively. The maximum predicted improvement in the hazard ratio for OS and PFS was 75% and 65%, respectively, and was predicted to be achieved within the range of Olara serum levels observed in the study. Baseline ECOG status and prior treatments were found to significant covariates for OS. No significant covariates were identified for PFS.

Conclusions: OS and PFS in STS patients receiving Dox alone or in combination with Olara were successfully described by the survival models developed in this study. Olara Cmin1 and Cavg showed a similar predictive role for Olara effect on PFS/OS. The survival models are consistent with a greater effect of Olara on OS than PFS. Maximum improvement in the OS HR was predicted to occur within the range of Olara serum levels achieved in the study.

References:
[1] Tap et al., J Clin Oncol 33, 2015 (suppl; abstr 10501).

II-56: *Salvatore D'Agate* Optimisation of weight-banded dosing regimens of amoxicillin in neonates and young infants with sepsis

Salvatore D'Agate and Oscar Della Pasqua
University College London, London, UK

Objectives: To assess the feasibility of a simplified regimen for amoxicillin in pre-term and term infants (0 - 59 days) with sepsis in resource-limited settings taking into account the impact of covariate factors on systemic drug exposure.

Methods: The approach was based on the adaptation of an existing model developed by Carlier et al [1] in which the PK of amoxicillin has been characterised in critically ill adults. To account for the effect of differences in size, the model was integrated with the extrapolation approach proposed by Zhao et al[2], which relies on allometric concepts. The impact of other relevant demographic and clinical covariate factors was then evaluated using data from recent efficacy trials in the target population, which also served as a reference for the purposes of our analysis. NLME modelling was performed using NONMEM V7.3. Model performance was assessed by diagnostic and GOF criteria. Clinical trial simulations were then implemented to explore the feasibility of a simplified dosing regimen was based on the assumption that comparable drug exposure should be attained across the overall patient population, irrespective of age, body weight or disease severity. Measures of exposure to amoxicillin included the plasma concentration vs. time profile, Cmin, Cmax, AUC vs. time curve and time above MIC (T>MIC). Given the clinical evidence of the relevance of T>MIC for amoxicillin, target concentration values were selected to maximise this parameter.

Results: Amoxicillin PK was best described by a two compartment model with first order absorption and elimination. Birth weight, post-natal age and serum albumin concentration were identified as significant covariates affecting amoxicillin clearance whereas body weight and sepsis (disease state) were found to affect the volume of distribution of central and peripheral compartments. Body weight showed a significant effect on the inter-compartmental clearance. The predicted exposure to amoxicillin in a cohort of virtual patients with demographic characteristics comparable to the reference trials shows that target levels can be achieved across the overall population by using fixed dose in combination with two weight bands, namely: 1) 250 mg for patients < 4.0 kg and 500 mg patients $\geq$4.0 kg.

Conclusion: A fixed dosing regimen will warrant target drug levels during the dosing interval, minimising the risk of sub-optimal exposure in patients with low body weight. Further evidence of the suitability of the proposed doses should be obtained by prospective evaluation of PK in target population.

References:

[1] Carlier M, Noe M, De Waele JJ, Stove V, Verstraete AG, Lipman J, Roberts JA. Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. The Journal of antimicrobial chemotherapy 2013; 68: 2600-8.
[2] Zhao W, Biran V, Jacqz-Aigrain E. Amikacin maturation model as a marker of renal maturation to predict glomerular filtration rate and vancomycin clearance in neonates.

II-57: *Andre Dallmann* Validation of a Population Physiologically-Based Pharmacokinetic Model for Pregnant Women

Andre Dallmann (1), Ibrahim Ince (2), Michaela Meyer (2), Thomas Eissing (2), Georg Hempel (1)
(1) University of Münster, Münster, Germany, (2) Bayer Technology Services, Systems Pharmacology CV, Leverkusen, Germany

Objectives: The goal of this study is to validate a physiologically-based pharmacokinetic (PBPK) model for the prediction of pharmacokinetics (PK) of small molecule drugs in pregnant women at different stages of pregnancy.

Methods: Based on a recent literature review on anatomical and physiological changes during pregnancy [1], a pregnancy population PBPK model has been developed using PK-Sim®/MoBi® [2]. In this model, the standard model structure of an adult woman was extended by 9 physiological compartments. These compartments are either specific to pregnancy (e.g. placenta and fetus) or become of specific relevance during pregnancy (uterus and breasts). To ensure a smooth transition from the non-pregnant to the pregnant state, organs and blood flows at the onset of pregnancy were scaled to non-pregnant levels. Populations of pregnant women were created using the organ scaling approach implemented in PK-Sim® [3]. The pregnancy population PBPK model was applied to predict the PK of multiple drugs at different stages of pregnancy. Prediction results were evaluated by comparison with experimentally observed literature data.

Results: The pregnancy population PBPK model successfully predicted the PK of all drugs at different stages of pregnancy. Compared to the non-pregnant state, maximum clearance changes of renally cleared drugs were observed in the early 2nd trimester with an increase of approximately 50%. The differences declined towards delivery, approximating values comparable to non-pregnant clearance levels. No changes in the activity of renal transporters involved in the clearance were necessary to correctly predict the experimentally observed PK. This indicates that the activity of these transporters remains essentially constant throughout pregnancy.

Conclusions: We successfully developed and validated a pregnancy population PBPK model at different stages of gestation for multiple small molecule drugs. PK changes in pregnant women could be fully attributed to pregnancy-related changes in relevant physiological parameters such as kidney volume and perfusion. Ultimately, this model can be applied to investigate *in silico* the PK of small molecule drugs and help design dosages e.g. for clinical trials in this vulnerable special population.

References:

[1] Dallmann, A., 2015, PAGE 24, Abstr 3456.
[2] Eissing, T. *et al.* (2011). A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. *Frontiers in physiology* 2: 1–10.
[3] Willmann, S. *et al.* (2007). Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. *Journal of pharmacokinetics and pharmacodynamics* 34(**3**): 401–431.

II-58: *Fabrizia D'Antonio* Effect of psychotic subtypes on cognitive trajectories in Alzheimer's disease Neuroimaging Initiative ADNI2.

Fabrizia D'Antonio (1,2), Julie Bertrand (3,4), Yucheng Sheng (5), Robert Howard (1), Suzanne Reeves (1,2)
(1)Division of Psychiatry - University College London - London (2) Department of Old Age Psychiatry - King's College London - London (3) 4 UMR 1137, Inserm - University Paris Diderot - Paris (4) University College London Genetic Institute (5) Department of Pharmaceutics - UCL School of Pharmacy - London

Objectives: The psychosis phenotype in Alzheimer's disease (AD) may be comprised of two subtypes: paranoid (persecutory delusions), and misidentification (misidentification phenomena ± visual and auditory hallucinations).Psychosis is associated with a faster speed of cognitive decline, but whether this effect is subtype dependent has not been explored. This study aim to model how psychotic subtypes impact cognitive trajectories, evaluated by AD Assessment Scale (Adas-cog), in the longitudinal dataset ADNI2.

Methods: ADNI2 participants categorised as late mild cognitive impairment or AD over a 4 years observation period were included in the analysis. Trajectories were fitted with simplified versions of the Richard's function (Samtani et al. 2012, Conrado et al. 2014). These models may allow to capture an inflection point beyond which the rate of decline reaches a plateau. Adas-cog being bounded between 0 and 70, we explored both a constant error model on the log-transformed observations and an extended logit error model. The psychosis effect on the progression rate parameter was explored as follows: "psychotic symptoms y/n", "delusion y/n", "hallucination y/n" and finally psychotic subtypes. Potential confounding covariates were also explored. Parameter estimation was performed using the SAEM algorithm implemented in the Monolix software (v4.3.3) and model selection was based on likelihood ratio test and visual predictive checks.

Results: Among the 528 patients in this analysis, there were 96 psychotic subjects, of whom 38 were pure paranoid subtype, 29 pure misidentifications subtype and 28 mixed subtype. Samtani's function with a constant error model fitted the data better. A correlation between Adas-cog at baseline and rate of progression was required to ensure model stability. The inflection point for the Adas-cog score trajectory was at 46.8 units, consistent with previous literature. The presence of psychotic symptoms significantly increased the rate of disease progression from 1.3 to 3.0% in ADAS-cog score per year ($P<0.001$). Misidentification subtype alone increased the rate from 1.3 to 2.8% ($P =0.021$), paranoid subtype was not significantly associated, but the presence of both psychotic subtypes (mixed) increased the rate from 1.3 to 3.9% ($P =0.0016$).

Conclusion: We quantified how presence of psychosis yield faster cognitive decline. Moreover, we showed how this effect is essentially associated with mixed and misidentification subtype.

References:

[1] Cook SE, Miyahara S, Bacanu SA, Perez-Madriñan G, Lopez OL, Kaufer DI, Nimgaonkar VL, Wisniewski SR, DeKosky ST, Sweet RA.. Psychotic symptoms in Alzheimer disease: evidence for subtypes. Am J Geriatr Psychiatry. 2003 Jul-Aug;11(4):406-13
[2] Reeves SJ, Gould RL, Powell JF, Howard RJ. Origins of delusions in Alzheimer's disease. Neurosci Biobehav Rev. 2012 Nov;36(10):2274-87
[3]Samtani MN, Farnum M, Lobanov V, Yang E, Raghavan N, Dibernardo A, Narayan V; Alzheimer's Disease Neuroimaging Initiative. An improved model for disease progression in patients from the Alzheimer's disease neuroimaging initiative. J Clin Pharmacol. 2012 May;52(5):629-44

[4]Conrado DJ, Denney WS, Chen D, Ito K. An updated Alzheimer's disease progression model: incorporating non-linearity, beta regression, and a third-level random effect in NONMEM. J Pharmacokinet Pharmacodyn. 2014 Dec;41(6):581-98.

II-59: *Pieter De Cock* piperacillin-tazobactam pharmacokinetics in critically ill children: implications on adequate dosing regimens

Pieter A.J.G. De Cock(1,2,3,4), Sven C. van Dijkman (4), Annick de Jaeger (4), Jef Willems (3), Mieke Carlier (5), Alain G. Verstraete (5,6), Joris R. Delanghe (5,6), Hugo Robays (1), Johan Vande Walle (7), Oscar E. Della Pasqua (4,8,9), Peter De Paepe (2

(1)Department of Pharmacy, Ghent University Hospital, Ghent, Belgium (2)Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium (3)Department of Paediatric Intensive Care, Ghent University Hospital, Ghent, Belgium (4)Leiden Academic Centre for Drug Research, Division of Pharmacology, Leiden, the Netherlands (5)Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium (6)Department of Laboratory Medicine, Ghent University Hospital, Ghent, Belgium (7)Department of Paediatric Nephrology, Ghent University Hospital, Ghent, Belgium (8)GlaxoSmithKline, Clinical Pharmacology and Simulation, Uxbridge, United Kingdom (9)Department of Clinical Pharmacology and Therapeutics, School of Pharmacy, University College London, London, United Kingdom

Objectives: The objective of this study was to investigate the pharmacokinetics of piperacillin and tazobactam in critically infants and children.

Methods: This pharmacokinetic study enrolled patients admitted to the paediatric intensive care unit in whom intravenous piperacillin-tazobactam was indicated (75 mg/kg q6h). Piperacillin/tazobactam concentrations were measured by a liquid chromatography-tandem mass spectrometry method. Population pharmacokinetic analysis (NONMEM) was conducted.

Results: Piperacillin and tazobactam blood samples were collected from 47 patients (median age: 2.83 years; range: 2 months - 15 years). A two-compartment model for piperacillin and tazobactam best described the data, in which allometric weight scaling and a Hill maturation function were added to scale for size and age. The typical population values of clearance for piperacillin and tazobactam were 4 L/h and 2.52 L/h for a typical child of 14 and 11 kg, respectively. Monte Carlo simulations demonstrated that an intermittent infusion of 75 mg/kg 4 hourly given over 1-2 hours or a loading dose of 75 mg/kg followed by a continuous infusion of 300 mg/kg/24h (based on the piperacillin component) were minimally required to achieve the piperacillin therapeutic target.

Conclusions: Standard intermittent dosing regimens are unlikely to achieve optimal piperacillin-tazobactam exposure in critically ill children with sepsis, thereby risking treatment failure.

II-60: *Miné De Kock* Pharmacokinetics of Sulfadoxine and Pyrimethamine for intermittent preventive treatment of malaria during Pregnancy and after delivery.

M de Kock (1), KI Barnes (1), MM Nyunt (2), I Adam (3), L Workman (1), P Denti (1)
(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa. (2) Johns Hopkins Malaria Research Institute, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America. (3) Department of Obstetrics and Gynaecology, University of Khartoum, Khartoum, Sudan.

Objectives: Sulfadoxine/pyrimethamine (SP) is recommended for intermittent preventative (IPT) treatment of malaria during pregnancy. In this work, we present a secondary analysis of data previously interpreted without population modelling [1] that was characterised by large between-site variability. This was explained in part by differences in sampling schedule, with some pharmacokinetic profiles only sparsely sampled. The aim of this study was to characterise the pharmacokinetics (PK) of SP in pregnancy and after delivery using nonlinear mixed-effects modelling, and explore the effect of predefined covariates to possibly explain some of the variability between sites.

Methods: 98 women, in four African countries, each received a single fixed dose combination of 75 mg of pyrimethamine and 1500 mg of sulfadoxine orally, as IPT during pregnancy and again several weeks after delivery. In Mali and Zambia, samples were collected before dosing and 3, 6, 12 hours and 1, 3, 7, 14, 21, and 28 days following dosing, during pregnancy and after delivery. In Mozambique and Sudan, samples were collected before dosing and on day 1, 2, 3, 7, 14, 21, 28, and 42 following dosing during pregnancy and after delivery only before dosing and 7 days following dosing. NONMEM 7.3 [2] was used to analyse the PK data. The effect of body size was taken into account using allometric scaling with total body weight at dosing [3]. Study site, age, anaemia, mg/kg dose, pregnancy status, gestation trimester, and time after delivery were tested as predefined covariates, using the objective function value, goodness of fit plots, and visual predictive checks to guide the model development.

Results: Clearance during pregnancy was 75.8% higher for sulfadoxine and 11.5% lower for pyrimethamine than after delivery. Clearance after delivery was found to change gradually, with the “pregnancy effect” becoming negligible after around 3 months. Haematocrit-based scaling of plasma to whole blood concentrations and allometric scaling explained some of the variability between study sites, but substantial site specific differences in the PK profiles of the individuals remained.

Conclusions: The dose of sulfadoxine during pregnancy should possibly be increased while pregnancy-related changes in pyrimethamine are not expected to be clinically relevant. Further research is necessary to elucidate whether dose optimisation, to address the underexposure to sulfadoxine in pregnant women, is necessary, viable and safe with the current fixed dose combination of SP.

References:

[1] Nyunt, M.M. et al. Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. Clin Pharmacol Ther. 87(2), 226-234 (2010).
[2] Beal, S. et al. NONMEM users guides (1989–2009). Ellicott City, MD, USA: ICON Development Solutions; 2009.
[3] Anderson, B. J. et al. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 48, 303–32 (2008).

II-61: *Bernardo de Miguel Lillo* Modeling the dynamics of alanine aminotransferase in advanced cancer patients treated with kahalalide F

Bernardo Miguel-Lillo (1,7), Belén Valenzuela (2,3), José Esteban Peris-Ribera (4), Jorge L. Iglesias (5), Vicente Alfaro (5), Arturo Soto-Matos (1,5), Juan José Pérez-Ruixo (6).
(1) Clinical Pharmacology, Pharma Mar, Colmenar Viejo, Madrid, Spain. (2) Platform of Oncology, Hospital Quirón Torrevieja. Torrevieja, Alicante, Spain. (3) Cathedra of Multidisciplinary Oncology. UCAM Catholic University of San Antonio, Murcia, Spain. (4) Pharmacy and Pharmaceutical Technology Department, Valencia University, Valencia, Spain. (5) Clinical Development, Pharma Mar, Colmenar Viejo, Madrid, Spain. (6) Model Based Drug Development, Janssen Research & Developments, Beerse, Belgium. (7) SGS Exprimo NV, Mechelen, Belgium.

Objectives: Reversible transient elevation of alanine aminotransferase (ALT) is observed after intravenous (iv) administration of kahalalide F (KF) in cancer patients. The aim of this study was to develop a pharmacokinetic-pharmacodynamic model to describe the transient elevation of ALT following different KF dosing schedules.

Methods: A precursor-dependent indirect pharmacodynamic response model (1) was used to characterize the ALT time course (data from 250 patients) using NONMEM (2) , where the transfer process of ALT from hepatocytes to plasma was stimulated by plasma KF concentrations. Potential effect of patient´s covariates was analyzed. Model evaluation was performed using visual predictive check and non-parametric bootstrap. Simulations were conducted to explore the role of dosing schedule on the incidence of severe ALT.

Results: The model differentiated between patients with (14%) and without (86%) ALT elevation. Baseline and terminal half-life for serum ALT were estimated to be 0.517 xULN and 45.5 h, respectively. Evaluated covariates did not significantly explain pharmacodynamic variability, but liver metastasis was associated with a 24% decrease in baseline serum ALT. The model evaluation evidenced an accurate prediction of the incidence of ALT grade 2 and $\geq$3. Simulations showed that time course of ALT depends on dose and dosing schedule, but not on the infusion duration.

Conclusions: The time course of ALT after KF iv infusion was adequately characterized by the model developed. According to simulations, the dosing schedule selected for phase II studies (650 µg/m² iv 1 h weekly) will not increase substantially the risk of severe ALT increase in cancer patients.

References:

[1] Fetterly GJ, Owen JS, Stuyckens K, Passarell JA, Zannikos P, Soto-Matos A, Izquierdo MA, Perez-Ruixo JJ Semimechanistic pharmacokinetic/pharmacodynamic model for hepatoprotective effect of dexamethasone on transient transaminitis after trabectedin (ET-743) treatment. Cancer chemotherapy and pharmacology. 2008;62(1):135-147.
[2] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.

II-62: *Mailys De Sousa Mendes* A physiologically based pharmacokinetic model for a drug metabolized by several CYP450 during pregnancy

Maïlys De Sousa Mendes
Paris V University

Objectives: Pregnant women can be exposed to numerous drugs during the gestational period. Due to obvious ethical reasons, *in vivo* studies are limited. Information about maternal drug exposure and drug transplacental transfer prior administration to pregnant women would be highly useful. We built a physiologically based pharmacokinetic (PBPK) model for a drug metabolized by the CYP3A4, 2B6 and 2D6, the nevirapine.

Methods: A whole body PBPK model was first developed in non-pregnant population and then in pregnant women for nevirapine drug. We implemented all physiological changes that can impact the pharmacokinetic as weight gain and plasma volume increase. Moreover we implemented enzymatic induction and renal clearance increase. Transplacental parameters estimated from *ex-vivo* human placenta perfusion experiments were implemented in the PBPK model in order to predict foetal PK. To validate the model, concentrations after drug administration were simulated for several dose regimens and populations, and then compared to observed concentrations [1].

Results: We predicted a clearance increase of 21 % and 38 % in late pregnancy after a single dose administration and at steady state respectively. These results are in accordance with literature data. The PBPK model successfully predicts the disposition for non-pregnant and pregnant populations. Parameters obtained from the *ex-vivo* experiments allowed the prediction of observed cord blood concentrations. Observed maternal to foetus AUC ratio was 0.75 and predicted maternal to foetus AUC ratio was 0.77.

Conclusions: Pregnancy PBPK models are useful tools to quantify *a priori* drug exposure changes during pregnancy for metabolized drugs. These models can be applied to evaluate alternative dosing regimens to optimise drug therapy during pregnancy. Moreover the integration of *ex-vivo* human placental perfusion parameters in a PBPK model should be a promising new approach for predicting human foetal exposure to xenobiotics.

References:

[1] Benaboud S, Ekouévi DK, Urien S, Rey E, Arrivé E, Blanche S, Gray G, Sim KL, Avit D, McIntyre J, Nerrienet E, Dabis F, Tréluyer J-M, Hirt D. Population pharmacokinetics of nevirapine in HIV-1-infected pregnant women and their neonates. Antimicrob Agents Chemother. 2011 Jan;55(1):331–7.

II-63: *Aurelia de Vries Schultink* Pharmacokinetics of MCLA-128 in cynomolgus monkeys and extrapolation to humans to support selection of first-in-human dose

Aurelia HM de Vries Schultink (1), Robert P Doornbos (2), Alexander BH Bakker (2), Setareh Shamsili (2), Mark Throsby (2), Jan H Schellens (1,3), Jos H Beijnen (1,3), Alwin DR Huitema (1)
(1) The Netherlands Cancer Institute, Amsterdam, the Netherlands, (2) Merus B.V., Utrecht, the Netherlands, (3) Utrecht University, Utrecht, the Netherlands

Objectives: MCLA-128 is a full length IgG1 bispecific monoclonal antibody (mAb) targeting receptor tyrosine kinases HER2 and HER3 to overcome HER3-mediated resistance to HER2 or EGFR targeted therapies. MAbs of the IgG1 subclass follow primarily linear clearance through cellular uptake followed by lysosomal degradation. The pharmacokinetics (PK) of mAbs are characterized by target mediated drug disposition, leading to saturation of the target and a co-existing nonlinear degradation. MCLA-128 was preclincally tested in cynomolgus monkeys to estimate PK parameters of MCLA-128 using a model based approach and to predict exposure to MCLA-128 in humans in order to support selection of first-in-human dose.

Methods: PK data was obtained from a single-dose toxicity study (n=6) and the first week of a repeated dose toxicity study (n=32) in cynomolgus monkeys. MCLA-128 was quantified in serum using a validated electrochemiluminescence immunoassay. PK parameters were estimated using NONMEM (v.7.3) and parameters were scaled to humans using allometric scaling. A two-compartment model with parallel linear and nonlinear elimination was tested. For model evaluation, parameter estimate plausibility, parameter precision, visual predictive checks and goodness of fit plots were examined. The safety margins for different proposed starting dose levels were obtained by dividing the AUC in cynomolgus monkeys at the NOAEL (no observed adverse effect level), which was found at the highest dose evaluated (100 mg/kg), by the predicted AUC in human.

Results: PK profiles were well described by a two-compartment model with parallel linear and nonlinear elimination pathways. Parameter estimates were scaled to 70 kg human. The estimated parameters were consistent with the general PK characteristics of therapeutic mAbs as expected based on the full length IgG1 format of MCLA-128 [1].
Proposed starting dose levels of 10 mg and 40 mg flat dose had associated safety margins of 6655 and 623, respectively.

Conclusions: MCLA-128 showed coexisting linear and nonlinear clearance pathways in cynomolgus monkeys. Based on calculated safety margins the proposed First-in-Human starting doses of 10 and 40 mg every three weeks have a large safety margin.

References:
[1] Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin. Pharmacokinet. 2010;49:633-59

II-64: *Brenda de Winter* Pharmacokinetics of Pentobarbital in Pediatric Status Epilepticus Patients

Julia M. Penning de Vries (1), Birgit C.P. Koch (2), Enno Wildschut (1), Brenda. C.M. de Winter (2), Matthijs de Hoog (1)
(1) Erasmus MC, Department Intensive Care, Sophia Children's Hospital; Rotterdam, (2) Erasmus MC, Department of Hospital Pharmacy, Rotterdam

Objectives: Status epilepticus (SE) is a life threatening event which requires immediate medical intervention. The overall mortality in children treated for refractory generalized convulsive SE is 16%-64% [1]. Little consensus consists regarding treatment of refractory SE and there are no randomized, blinded studies in either adults or children. Pentobarbital is the last resource to treat SE. In daily practice dosing is adjusted based on EEG and pentobarbital drug level. However, too low or too high drug levels are often seen. The aim of this study was to design a pharmacokinetic model of pentobarbital, which can be incorporated in therapeutic drug monitoring.

Methods: The design of the study was a retrospective, single-center analysis of medical records of all consecutive pediatric patients who received pentobarbital-coma for refractory generalized convulsive status epilepticus from 2007 through 2012 at the Department of Pediatric Intensive Care, Sophia Children's Hospital, Rotterdam for the primary dataset and between 2013 and February 2015 for de validation set. Inclusion: age 1 week - 18 years, exclusion all patients receiving pentobarbital for other reasons than SE. For pharmacokinetic analysis NONMEM® version 7.2 was used. Demographic and laboratory parameters were evaluated as covariates. Allometric scaling was used to adjust for differences in bodyweight using a factor of 0.75 for clearance and 1 for volume of distribution. The parameters of the final model were introduced in MW-Pharm to validate for use in daily practice.

Results: 16 patients were included in the primary set (median age 76 [17-1363] days, median weight 5.4 [3-19] kg. Mean loading dose was 8.8 [0-15.65] mg/kg, mean maintenance dose 4 [1-10] mg/kg/h. In the validation set 6 patients were included (median age 120 [63-460] days, median weight 6.1 [6-10] kg). Mean loading dose was 15.4 [15-16.6] mg/kg and mean maintenance dose 4.5 [3-7] mg/kg/h. The data was best described in a two-compartment model (V1 0.89 L/kg (58% BSV), V2 1.46 L/kg, with clearance of 5.12 L/h (45% BSV). In children below 1 year, clearance was increased. NPDE of the validation dataset using the final model showed accurate results. Finally, prediction of the final data point of the validation set and comparing it with the real data set, resulted in all predicted data being <20% different than the real data.

Conclusion: The PK model was validated and has been incorporated in MWPharm to be used in daily practice.

References:
[1] Kim SJ, Lee DY, Kim JS. Pediatr Neurol 2001;25:217–220.

II-65: *Wilbert de Witte* High drug-target association rates increase the duration of in vivo target occupancy

W.E.A. de Witte, M. Danhof, P.H. van der Graaf, E.C.M. de Lange
Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands

Objectives: Drug-target binding kinetics is an important determinant of the time course of target occupancy and low drug-target dissociation rates (koff) are increasingly used as a selection criterion in drug discovery to obtain a prolonged duration of drug action[*1*–*3*]. However, drug-target binding can also influence the pharmacokinetics of a drug in blood and at the tissue and cellular level. This interaction is commonly referred to as "Target-Mediated Drug Disposition" (TMDD)[*4*, *5*], "rebinding"[6] or "diffusion-limited binding". Our objective is to generate a comprehensive understanding into the influence of drug-target binding kinetics on the time course of target occupancy *in vivo*.

Methods: Available mathematical models provide a basis to predict the change in target occupancy over time, but do not provide a direct insight into the relative contributions of the pharmacokinetic and drug-target binding parameters. Mathematical analysis and simulations on the basis of these models were used to gain insight into the role of drug-target binding kinetics as a determinant of the target occupancy profile. Model simplification was achieved by assuming that the decrease in target occupancy is influenced mostly by the slowest step, which can be dissociation, distribution or elimination.

Results: Our analysis of a one-compartment model with target binding and a two compartment model with target binding in the peripheral compartment demonstrates that the duration of target occupancy can be prolonged by high drug-target association (kon) and low drug distribution rate constants. Moreover, this analysis identifies a number of algebraic expressions that describe the negative log-linear slope of the target occupancy versus time curve and that constitute a basis to identify the rate-limiting step in the decrease of target occupancy.

Conclusions: In contrast to the current focus on koff, optimising the duration of target occupancy should be based on the values of both koff and kon, according to a set of algebraic equations that integrate pharmacokinetics and drug-target binding. We propose the use of the derived negative slope of target occupancy *versus* time curve for prediction of the duration of target occupancy together with the identification of the rate-limiting step, to inform on the most relevant parameters for drug discovery.

References:
[1] F. Schiele, P. Ayaz, A. Fernández-Montalván, A universal, homogenous assay for high throughput determination of binding kinetics. *Anal. Biochem.* **468**, 42–49 (2014).
[2] S. J. Ramsey, N. J. Attkins, R. Fish, P. H. van der Graaf, Quantitative pharmacological analysis of antagonist binding kinetics at CRF1 receptors in vitro and in vivo. *Br. J. Pharmacol.* **164**, 992–1007 (2011).
[3] G. Dahl, T. Akerud, Pharmacokinetics and the drug-target residence time concept. *Drug Discov. Today*. **18**, 697–707 (2013).
[4] P. Dua, E. Hawkins, P. van der Graaf, A Tutorial on Target-Mediated Drug Disposition (TMDD) Models. *CPT Pharmacometrics Syst. Pharmacol.* **4**, 324–337 (2015).
[5] G. Levy, Pharmacologic target-mediated drug disposition. *Clin. Pharmacol. Ther.* **56**, 248–252 (1994).
[6] G. Vauquelin, S. Bostoen, P. Vanderheyden, P. Seeman, Clozapine, atypical antipsychotics, and the

benefits of fast-off D2 dopamine receptor antagonism. *Naunyn. Schmiedebergs. Arch. Pharmacol.* **385**, 337–72 (2012).

II-66: *Amelia Deitchman* Tetracycline against Pseudomonas aeruginosa: Pharmacokinetic/Pharmacodynamic Modeling of In Vitro Time-Kill Curves

Amelia N. Deitchman (1), Johannes Kast (1), Hartmut Derendorf (1)
(1) University of Florida, Gainesville, FL, USA

Objectives: Together, tigecycline (TIG) and tetracycline (TET) have displayed augmented in vitro activity against *Pseudomonas aeruginosa* [1]. The goal of this research is to develop a PK/PD model that describes the observed effects of TET against *P. aeruginosa* in *in vitro* static time-kill experiments incorporating results from resistance testing and accounting for potential drug degradation.

Methods: *In vitro* static time kill curves of 0.25, 0.5, 1, 2, 4, and 8 XMIC were performed in triplicate for TET (MIC 16 mg/L) against *P. aeruginosa*. Concentrations of bacteria were quantified at 0, 2, 4, 6, 8, 10, 12, 16, and 24 hours [2]. Resistance testing was performed by plating aliquots on 3X MIC drug-containing agar plates after 24 hours of varying levels of TET exposure. PK/PD modeling of time-kill curves was conducted using NONMEM (Version 7.3.0). Various one- and two- bacterial subpopulation models were fitted and evaluated based on change in objective function value (OFV), goodness of fit plots, and visual predictive checks to explore aspects of drug effect, drug degradation, and delay in drug effect. Models for incorporating resistant subpopulations or adaptive resistance were considered based on experimental results.

Results: TET time kill curve data were best described using a model including susceptible and persistent resting subpopulations of bacteria. A sigmoidal Emax model best described the drug effect (EC50 24.4 mg/L tetracycline HCl, Hill factor 1.22, maximal kill rate constant 3.39 h^{-1}). While delay of drug effect did not improve model fit, drug degradation did allow for better description of the data. Resistance was not considered in the modeling process, as TET resistance was not observed at any tested concentrations at 24 hours.

Conclusions: The developed model describes the effect of TET well against *P. aeruginosa* over time for various drug exposures and is informed by additional resistance testing. A similar approach will investigate and incorporate resistance for TIG and the combination of TIG and TET. A final model describing the effects of each drug, alone and in combination, will be used, with published clinical PK data/models, to simulate and evaluate potential dosing regimens for the treatment of *P. aeruginosa*.

References:

[1] Deitchman AN, Singh RP, Mukker JK, Sy SK, Zoehner A, Derendorf H. Exploring *In Vitro* Antipseudomonal Activity Of Synergistic Tigecycline-Tetracycline Combinations. ASCPT Poster Presentation 2015. New Orleans, LA. Clin Pharmacol Ther. 2015 Feb; 97(S1):S26.
[2] Deitchman A, Singh R, Zoehner A, Derendorf H. *In Vitro* Pharmacodynamics of Tigecycline and Tetracycline Combinations against *Pseudomonas aeruginosa*. ECCMID Poster Presentation 2015. Copenhagen, Denmark.

Acknowledgement: This research is funded by a University of Florida Clinical and Translational Science Institute Pilot Project Award.

II-67: *Laurence Del Frari* Predicting human pharmacokinetics of monoclonal antibodies by allometric translation from preclinical data: a case study

Laurence Del Frari (1), Eric Didier (1)
(1) Pierre Fabre Médicament, Centre de R&D, Toulouse, France

Objectives: F50067 is a CXCR4 receptor antagonist humanised monoclonal antibody developed by Pierre Fabre Laboratories for the treatment of Acute Myeloid Lymphoma (AML) and Multiple Myeloma (MM). In order to support the dose and dosing selection in human patients, a pharmacokinetic (PK) model was developed using PK data collected in monkeys (NHP).

Methods: Data were obtained from 4 studies in NHP after single IV administration in the range from 1 to 120 mg/kg involving 50 animals and 353 concentrations. The population PK analysis was performed by non linear mixed effects modelling approach using NONMEM 7.2 with FOCE + interaction estimation. The model building and the selection of the best model was conducted using differences in Objective Function Values, Visual inspection of Goodness Of Fit Plots and Visual Predictive Checks (VPC). Then translational approach to predict the PK in human was done through allometric scaling of the clearance and volume of distribution, with allometric coefficients tested between 0.75 and 1 in order to provide an adequate range of predictions for the PK in human [1,2].

Results: The developed PK model in NHP displayed a dual clearance, with a non linear component and a linear component allowing to take into account the observed target mediated disposition [3]. VPC showed that the model described adequately the observations and allowed simulations. In MM and AML patients, it appears that the observed PK is accurately predicted with a PK model using allometric scaling of 1 on the volume of distribution and the clearance.

Conclusions: In spite of its target mediated disposition behaviour, which could have been a source of imprecision in the estimates, allometric scaling from NHP to human allowed to accurately predict the PK in human of a monoclonal antibody targeting a membrane bound receptor such as CXCR4. This allometric translation of a PK model allowed to appropriately select a once weekly dosing regimen in the clinical program.

References:
[1] Dong J. Q. et al. Quantitative prediction of human pharmacokinetics for monoclonal antibodies - retrospective analysis of monkey as a single species dor first-in-human prediction. Clin Pharmacokinet (2011) 50:131-142.
[2] Lobo E. L. et al. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci (2004) 93:2645-2668.
[3] Gibianski L. et al. Approximations of the target-mediated drug disposition model and identifiability of model parameters. Journal Pharmacokinet Pharmacodyn (2008) 35:573-91.

II-68: *Ivan Demin* Guidance on dose-finding studies for biostatisticians and pharmacometricians: a Pharmacometrics perspective

Ivan Demin (1), Baldur Magnusson (1), Oliver Sander (1), Bjoern Bornkamp (1), Stephan Koehne-Voss (1), Bjoern Holzhauer (1), Michael Looby (1), Frank Bretz (1)
(1) Novartis Pharma AG, Switzerland

Objectives: Finding the best dose and regimen is a key aspect of clinical development programs and quantitative line functions, such as biostatistics, pharmacometrics (PMX), and clinical pharmacology can greatly contribute here. Questions around the design and analysis of phase 2b dose and regimen finding studies are often complex and many aspects are to be considered. Within a large pharmaceutical organization guidance for quantitative input on dose finding studies can support statisticians and pharmacometricians with their input to dose finding studies, improve collaboration of quantitative line functions, and overall increase quality of dose finding studies.

Methods: At Novartis "Guidance for design and analysis of phase 2b dose and regimen finding studies" was developed for biostatisticians and pharmacometricians. The objectives of the guidance were to 1) discuss key quantitative aspects of the design and analysis of dose-finding studies relevant for biostatistics and PMX; and 2) to highlight opportunities for collaboration between quantitative line functions such as biostatistics, PMX and clinical pharmacology. This poster presents the PMX perspective.

Results: The resulting guideline consists of five sections: 1) Scope, 2) Objectives of Phase 2b dose-finding studies, 3) Prior data to inform the design of phase 2b, 4) Designing phase 2b, and 5) Analysing phase 2b. In each section quantitative aspects of dose finding studies are discussed and different settings for dose-finding are considered. Key aspects of the analysis of phase 2b and subsequent design of phase 3 are addressed. At each stage opportunities for potential collaboration between PMX and biostatistics are highlighted.

From PMX perspective key elements of the study protocol for the dose finding study include selection of dose range, dose groups, loading and maintenance doses, duration of washout, and assessments for dose-exposure-response (D-E-R) modeling. At the analysis phase, D-E-R modelling is often performed as a secondary or exploratory analysis. Findings of primary D-R analysis and exploratory D-E-R analysis should be aligned before sharing the result with the project team.

Conclusion: Throughout design and analysis of phase 2b studies it is crucial to optimize quantitative input and to maintain close collaboration between PMX and biostatistics. This process can be facilitated by a guidance for dose-finding studies for biostatisticians and pharmacometricians.

II-69: *Paolo Denti* Population Pharmacokinetics of Levofloxacin in South African children.

Paolo Denti (1), Anthony Garcia-Prats (2), Heather Draper (2), Lubbe Wiesner (1), H. Simon Schaaf (2), Helen McIlleron (1), Anneke Hesseling (2)
(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa (2) Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa

Objectives: The fluoroquinolone levofloxacin is the levo-isomer of ofloxacin and is widely used for treatment and prophylaxis of multi-drug-resistance-tuberculosis (MDR-TB). Limited data on its PK is available in children. The aim of this study is to characterise levofloxacin PK in children to optimise dosing.

Methods: 109 South African children, median age 2.1 yr (range 0.3–8.7) and weight 12 kg (6–22), received daily levofloxacin within a study on MDR-TB treatment/prophylaxis. Samples were collected before dosing and at 1, 2, 4, 6, and 8 hours post-dose. Children received 15 or 20 mg/kg, with exact dosing on the day of PK sampling. Smaller children received crushed tablets, often using a nasogastric tube. NONMEM 7.3 with FOCE-I was used to interpret the PK data. The effect of body size was captured with allometric scaling [1], while the effect of age, HIV status, treatment vs. prophylaxis, and drug administration procedure were evaluated. Simulations from the final model were used to optimise doses across different weight bands, targeting adult exposure.

Results: Levofloxacin followed 2-compartment kinetics with 1st-order elimination and absorption through transit compartments [2]. After inclusion of allometric scaling, which substantially improved the fit, the model could characterise age-driven maturation of CL with an effect reaching 50% around 2 months after birth. CL in a 12 kg, 2-year-old child was estimated 4.7 L/h. The use of nasogastric tube increased the rate of absorption, but no significant effect on bioavailability could be detected. HIV positive children were found to have 16% slower CL. Levofloxacin exposures in this cohort of children were significantly lower than previously reported in adults dosed 1000 mg daily (a similar mg/kg dose): 45 vs. 129 mg·h/L [3]. Only part of this difference could be explained by allometric scaling. To achieve exposures similar to adults a dose of 50 mg/kg would be required, with smaller children receiving higher mg/kg doses, except very young children with immature CL (<1 yr old).

Conclusions: Consistently with reports in other paediatric populations [4], children achieve levofloxacin exposures considerably lower than adults using the same mg/kg dose, and this difference cannot be fully explained by allometric scaling. Our report of slightly higher exposure in HIV positive children, of unlikely clinical significance, would need further investigation in other studies.

References:

[1] B. J. Anderson and N. H. G. Holford, “Mechanism-based concepts of size and maturity in pharmacokinetics.,” Annu. Rev. Pharmacol. Toxicol., vol. 48, pp. 303–32, Jan. 2008.
[2] R. M. Savic, D. M. Jonker, T. Kerbusch, and M. O. Karlsson, “Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies.,” J. Pharmacokinet. Pharmacodyn., vol. 34, no. 5, pp. 711–26, Oct. 2007.
[3] C. a. Peloquin, D. J. Hadad, L. P. D. Molino, M. Palaci, W. H. Boom, R. Dietze, and J. L. Johnson, “Population pharmacokinetics of levofloxacin, gatifloxacin, and moxifloxacin in adults with pulmonary tuberculosis.,” Antimicrob. Agents Chemother., vol. 52, no. 3, pp. 852–7, Mar. 2008.

[4] S. R. Mase, J. A. Jereb, D. Gonzalez, F. Martin, C. L. Daley, D. Fred, A. Loeffler, L. Menon, S. B. Morris, R. Brostrom, T. Chorba, and C. A. Peloquin, “Pharmacokinetics and Dosing of Levofloxacin in Children Treated for Active or Latent Multidrug-Resistant Tuberculosis, Federated States of Micronesia and Republic of the Marshall Islands,” Pediatr. Infect. Dis. J., p. 1, Dec. 2015.

II-70: *Christiane Dings* Pharmacokinetic and Pharmacodynamic Modeling of Acetylsalicylic Acid and its Major Metabolite Salicylic Acid

Christiane Dings (1) and Thorsten Lehr (1)
(1) Clinical Pharmacy, Saarland University, Saarbruecken, Germany

Objectives: Acetylsalicylic acid (ASA) is a well-known antipyretic drug and has been studied and used for its anti-thrombotic effect since the 1960s [1]. However, there is little knowledge about the pharmacokinetic/pharmacodynamic (PK/PD) relationship between ASA and platelet aggregation. Therefore, the aim of the work was to develop a PK/PD model of ASA and its major metabolite salicylic acid (SA) including thromboxane B2 (TxB2) as a biomarker for the antithrombotic effect of ASA.

Methods: PK and PD data was digitized from a study comparing PK and PD after doses of 5 to 80 mg ASA as instant release (IR) and 20 to 325 mg ASA as extended release (ER) formulations in 50 volunteers [2]. The data included 70 and 85 mean plasma concentrations of ASA and SA, respectively, and 77 mean measurements of TxB2 inhibition. The model was evaluated using digitized data from another PK/PD study of ASA [3]. Deterministic simulations were performed to investigate different treatment regimens ensuring sufficient inhibition of the platelet aggregation throughout the day (>95% TxB2 inhibition at steady-state) [3]. Modeling and simulation was performed using NONMEM (version 7.2.0) without interindividual variability, but considering residual variability.

Results: For ASA and SA a one- and two-compartment model, respectively, described the pharmacokinetics best. A compartment between the absorption compartment and the central compartments of ASA and SA was included to describe the presystemic metabolism and pharmacodynamic effect of ASA. All absorption, distribution and elimination processes of ASA and SA were described as first-order processes. TxB2 levels were described by a turnover model with zero-order input, first-order output. Under ASA treatment a second-order elimination depending on ASA and TxB2 levels was incorporated. The model successfully predicted the plasma TxB2 levels of the evaluation dataset. Simulations revealed that the administration of 97 mg (IR) twice daily and 169 mg (ER) once or 49 mg twice daily resulted in a sufficient platelet aggregation. Peak ASA plasma levels ensuring sufficient platelet inhibition were lower for the ER formulation.

Conclusion: A PK/PD model for ASA and its major metabolite SA was presented for the first time. The model demonstrated a good predictive performance. Deterministic simulations confirmed an advantage of the ER formulation over the IR formulation.

References:
[1] Weiss H J et al. The discovery of the antiplatelet effect of aspirin: a personal reminiscence. Journal of Thrombosis and Haemostasis (2003), 1(9): 1869-1875.
[2] Patrick J et al. A randomized trial to assess the pharmacodynamics and pharmacokinetics of a single dose of an extended-release aspirin formulation. Postgraduate Medicine (2015), 127(6):573-80.
[3] Nagelschmitz J et al. Pharmacokinetics and pharmacodynamics of acetylsalicylic acid after intravenous and oral administration to healthy volunteers. Clinical Pharmacology: Advances and Applications (2014), 6: 51–59.

II-71: *Aris Dokoumetzidis* A PBPK model for Tc99m-Tetrofosmin in humans from SPECT imaging data.

Liana Kormpili, Sofia Antimisiari1, Aris Dokoumetzidis
Department of Pharmacy University of Patras, Department of Pharmacy University of Athens, Greece

Objectives: To develop a PBPK model for the radiopharmaceutical Tc99-Tetrofosmin in humans from literature SPECT imaging data in order to extrapolate dosing to children.

Methods: Literature data from humans [1] of Tc99m-Tetrofosmin distribution were available for blood and compact organs, i.e. heart, lung, liver, gallbladder, kidney, thyroid and GI. The organs had been measured by pixel counting from imaging data and included 7 time points up to 24 h. Also rat data [2] were used for other tissues, i.e. muscle and fat, but with only 3 available time points, while distribution in the brain is negligible as the drug is known not to cross the BBB. Blood data were fitted to an empirical multi-exponential model to be used as a forcing function for open loop tissue models. One- and Two-compartment tissue models were considered and the partition coefficients, permeability parameters as well as clearance for kidneys and liver were estimated while physiological parameters were taken from literature [3]. Model selection was performed by visual inspection and goodness of fit. Finally, a closed loop model was constructed and parameters were re-estimated by fitting the model to all the data at once. A sensitivity analysis was carried out for the values of the less certain parameters, the ones from rats. The model was scaled to pediatric patients of various ages. Appropriate children doses were chosen in the basis that the profiles in the heart and the blood for children matched closely the ones of adults.

Results: A bi-exponential function was found to describe best the blood data and was used as a forcing function for the tissue open loop models. Two compartment tissue models were used for most tissues except the ones with only rat data available due to few samples. In most tissues the partition coefficient values were found to be extremely high due to binding of the drug to mitochondria, e.g. for the heart 130 (SE: 9.7%). The closed loop model was found to describe sufficiently the data, including the blood. Sensitivity analysis showed negligible dependence of the model output on fat distribution, possibly due to lack of mitochondria in this tissue. A per kilogram dosing as a fraction of the adult dose (activity of 250-400 MBq) seemed to be adequate for children.

Conclusion: A PBPK model predicted children doses of Tc99-Tetrofosmin. The model was developed from human data for most tissues.

References:
[1] Higley B, Smith FW, Smith T, Gemmell HG, Das Gupta P, Gvozdanovic DV, Graham D, Hinge D, Davidson J, Lahiri A. Technetium-99m-1,2-bis[bis(2-ethoxyethyl) phosphino]ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. J Nucl Med. 1993 Jan;34(1):30-8.
[2] Kelly JD, Forster AM, Higley B, Archer CM, Booker FS, Canning LR, Chiu KW, Edwards B, Gill HK, McPartlin M, et al. Technetium-99m-tetrofosmin as a new radiopharmaceutical for myocardial perfusion imaging. J Nucl Med. 1993 Feb;34(2):222-7.
[3] Kawai R, Mathew D, Tanaka C, Rowland M. Physiologically based pharmacokinetics of cyclosporine A: extension to tissue distribution kinetics in rats and scale-up to human. J Pharmacol Exp Ther. 1998 Nov;287(2):457-68.

II-72: *Thomas Dorlo* Translational PKPD modeling framework to assess the predictive performance of a preclinical visceral leishmaniasis hamster model

Thomas P.C. Dorlo (1,2), Louis Maes (3), Mats O. Karlsson (1), Stéphanie Braillard (4), Charles Mowbray (4)
(1) Dept. Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Div. Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, the Netherlands; (3) Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; (4) Drugs for Neglected Diseases initiative, Geneva, Switzerland

Objectives: Efficacy of novel compounds against the parasitic neglected tropical disease visceral leishmaniasis (VL) is typically assessed by reduction of splenic or hepatic intra-macrophageal *Leishmania* parasite burden in a Golden hamster infection model. Selection of adequate clinical dosing regimens based on these experiments is difficult, since the predictive value of this model remains unassessed. The aim of this study was to develop a translational framework to incorporate and model available preclinical PK and PD data of the oral antileishmanial drug miltefosine, derive appropriate PKPD targets, and assess their predictive performance by comparing PK target attainment in human VL patients.

Methods: First, a population PK model for miltefosine was developed on data from 36 healthy hamsters. Animals were treated with various single and multiple (5 day) p.o. dose regimens between 5 and 40 mg/kg/day. Subsequently concentration-time curves and secondary PK parameters for both free and total concentrations were simulated for *L. infantum*-infected hamsters in 2 early curative studies. PD endpoint in these studies was Leishman-Donovan Unit (LDU), which is representative for the total parasite burden, in liver and spleen of each animal at 14 days post-treatment. Exposure-response curves were fitted using 4-parameter log-logistic models. PK analyses and simulations were performed in NONMEM 7.3 and PKPD using the 'drc'-package in R.

Results: Miltefosine PK in hamsters could be described using a 1 compartment model, with various non-linearities characterized. Exposure-response curves for various PK parameters ($AUC_{0\text{-}14d}$, Time>IC_{50}, etc.) for both total and free miltefosine were successfully fitted. Various PK targets corresponding with 50%, 95% and 99% reduction of the parasite burden were calculated for each PKPD relationship. The probability of PK target attainment in human patients, accounting for species differences in protein binding, were compared to clinical outcome. Free $AUC_{0\text{-}14d}$ associated with 99% LDU reduction in hamster corresponded best with the observed fraction of human patients reaching this target in relation to clinical outcome.

Conclusions: For the first time PKPD relationships were quantified in *Leishmania*-infected hamsters. The translational framework may be a valuable tool to establish the best preclinical model and targets for drug discovery for leishmaniasis and help in the design of future first-in-human clinical trials.

II-73: *Anne-Gaelle Dosne* Robust QT prolongation assessment using model-averaging

Anne-Gaëlle Dosne (1), Martin Bergstrand (1), Mats Karlsson (1), Didier Renard (2), Günter Heimann (2)
(1) Uppsala University, Sweden, (2) Novartis Pharma AG, Basel, Switzerland

Objectives: TQT studies are pivotal safety studies which assess whether a drug prolongs the QT interval by 10 ms or more. Model-based estimation of the drug-induced QT prolongation at the estimated mean maximum drug concentration could increase efficiency over the currently used intersection-union test. However, robustness against model misspecification needs to be guaranteed in pivotal settings. The objective of this work was to develop an efficient, fully pre-specified model-based inference method for thorough QT studies where type I error is controlled.

Methods: The proposed estimator of the concentration-response relationship consisted of the weighted average of a parametric (linear) and a nonparametric (monotonic I-splines) estimator. Three alternatives were tested for estimating the weight of each estimator, based on the global Mean Integrated Square Error (MISE, as adapted from [1]), on the local MISE ([1]) or on the Bayesian Information Criteria (BIC). TQT studies were simulated to assess the performance of the methods under 24 scenarios with varying drug effect models (linear, Emax, sigmoid Emax and quadratic) and noise levels (sd of QTc 3.5-15 ms, 50 or 100 IDs).

Results: Model-averaging using global MISE weights was found to be an adequate method for TQT analysis. The proportion of studies wrongly concluding to the absence of QT prolongation was below 5% in all but 2 scenarios. Bias in estimated QT prolongation was small (+0.33 ms on average) and conservative 83% of the time under a true drug effect of 10 ms. Relative increases in power compared to the nonparametric method were 30% on average, while decreases in power compared to the parametric method were mostly below 10%.

Conclusions: An efficient, fully pre-specified model-based inference method for TQT studies where type I error is controlled was developed. This methodology could also easily be applied to QT assessment outside of TQT studies, for example in early phase I studies.

Acknowledgements: This work was supported by the DDMoRe (www.ddmore.eu) project and the FP7-HEALTH-2013-602552.

References:
[1] Yuan Y, Yin G, *Dose-Response Curve Estimation: A Semiparametric Mixture Approach*. Biometrics, 2011. 67: p. 1543–1554.
[2] Ramsay JO, *Monotone Regression Splines in Action*. Statistical Science, 1988. 4(5):p. 421-465.

II-74: *Erwin Dreesen* Anti-drug antibodies, low serum albumin and high C-reactive protein increase infliximab clearance in patients with inflammatory bowel disease: a population pharmacokinetic study of the TAXIT trial

Erwin Dreesen (1), Niels Vande Casteele (1), Sophie Tops (1), Séverine Vermeire (2), Ann Gils (1)
(1) Department of Pharmaceutical and Pharmacological Sciences, University of Leuven, Belgium (2) Department of Gastroenterology, University Hospitals Leuven, Belgium

Objectives: Infliximab (IFX, Remicade®) is an intravenously administered chimeric anti-tumor necrosis factor-alpha monoclonal antibody and is effective for treating patients with Crohn's disease (CD) and ulcerative colitis (UC). The Trough concentration Adapted infliXImab Treatment (TAXIT) trial was the first prospective study to show that targeting IFX trough concentrations between 3 and 7 µg/mL in responder patients on maintenance therapy leads to better outcome and a lower risk for loss of response.[1] Insight in the factors accounting for inter-individual variability (IIV) in pharmacokinetics (PK) in the dataset is lacking. Our aim was to identify key covariates that explain the IIV in IFX PK.

Methods: PK data originated from 263 patients with CD and UC included in the 1-year TAXIT trial. IFX trough concentrations before each administration and unbound anti-drug antibody (ADAb) titers were assessed using in-house developed ELISAs.[2] Relevant patient demographic, serological, genetic and clinical data were collected prospectively. Data were evaluated using population PK modeling (NONMEM® 7.3).

Results: IFX concentrations (n=2,429) from 263 patients were evaluated. Eighteen patients were identified with unbound ADAbs at one or more time points. IFX PK was best described using a one-compartment model with time-varying immunogenicity effect on linear clearance and an additive error model. Typical clearance was 0.581 L/day and typical volume of distribution was 14.2 L based on the final covariate model. Covariate analysis showed that IFX clearance was higher for male subjects, when serum albumin was low and when C-reactive protein (CRP) was high ($p<.001$). IFX clearance was typically 27.8 times higher when ADAbs were detected. The estimated effective half-life of IFX was approximately 17 days and less than 1 day when ADAbs were present. The identified covariates explained 21% of the IIV in IFX clearance. Remaining IIV in clearance was 35% and eta shrinkage was 3%.

Conclusions: A population PK model was developed, taking into account time-varying immunogenicity and patient factors. IFX clearance increases in the presence of ADAbs and in an active inflammatory state, represented by a decrease in serum albumin and an increase in CRP. Adapting the dosage regimen based on these covariates may allow more precise individualized dosing and improve outcome for patients with CD and UC.

References:
[1] Vande Casteele N, Ferrante M, Van Assche G, *et al*. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology (2015) 148(7):1320-9.
[2] Vande Casteele N, Buurman D, Sturkenboom M, *et al*. Detection of infliximab levels and anti-infliximab antibodies: A comparison of three different assays. Aliment Pharmacol Ther (2012) 36(8):765-71.

II-75: *Stefanie Drescher* An Integrated Model for Glucose and Insulin Regulation in Bariatric Surgery Patients following Intravenous Glucose Tolerance Test

Stefanie K. Drescher (1), Raja Venkatasubramanian (1), Paul Coen (2), Bret Goodpaster (2), Mirjam N. Trame (1)

(1) Center for Pharmacometrics and Systems Pharmacology, Dept. of Pharmaceutics, University of Florida, Orlando, FL, USA, (2) Translational Research Institute for Metabolism & Diabetes, Orlando, FL, USA

Objectives: Gastric Bypass Surgery (GBS) is a common treatment option for severe obesity. GBS induces weight loss but also improves glucose control by reducing muscle and liver insulin resistance and improving β-cell function [1,2]. Exercise is also effective at improving glucose control in GBS patients. So far these changes have not been quantitatively described by an integrated glucose-insulin model. Our objective was to develop an intravenous glucose tolerance test (IVGTT) model to predict improvements in insulin and glucose regulation in patients following GBS alone and with a 6-month exercise intervention.

Methods: Data from GBS patients with (n=60; treatment group) and without (n=59, control group) regular exercise after GBS were available from a previously conducted RTC [3]. IVGTT was conducted for the first time directly after bariatric surgery prior to any exercise intervention and repeated after a six month intervention period with and without exercise. The randomized controlled physical activity intervention was defined as minimum three and maximum of five exercise sessions weekly. A previously developed IVGTT model by Silber et al. [4] was used as a starting point. Disease progression was included and tested on varies parameters to evaluate and compare differences in glucose and insulin regulation between the control and the exercise group post GBS.

Results: The developed quantitative model was able to adequately describe the insulin-glucose-homeostasis in all subjects after IVGTT. Subjects in both groups, control and exercise, were found to overall have improved insulin dependent glucose clearance on their second visit. Additionally, subjects in the exercise group were found to have better insulin dependent glucose clearance and improved feedback to glucose production when compared to subjects in the control group. This was seen in a faster return of glucose levels after administration of intravenous glucose.

Conclusions: Based on clinical observations, a quantitative model was built to describe the interaction between glucose and insulin simultaneously in GBS patients after IVGTT. The results indicate that GBS has a positive influence on glucose-insulin-regulation and that additional exercise post GBS will result in further improvements. For the first time an IVGTT model was developed in post GBS patients helping to improve our understanding of the insulin-glucose-homeostasis in this patient population.

References:

[1] Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444 (7121): 881–7
[2] Pok E-H, Lee W-J. Gastrointestinal metabolic surgery for the treatment of type 2 diabetes mellitus. World J Gastroenterol WJG. 2014; 20(39): 14315–28
[3] Coen PM, Tanner CJ, et al. Clinical trial demonstrates exercise following bariatric surgery improves insulin sensitivity. J Clin Invest. 2015; 125(1):248-257
[4] Silber H-E, Jauslin P-M, et al. An Integrated Model for Glucose and Insulin Regulation in Healthy Volunteers and Type 2 Diabetic Patients Following Intravenous Glucose Provocations. Journal of Clinical Pharmacology, 2007; 47: 1159-1171

II-76: *Hélder Duarte* Amikacin in premature newborn: a new therapeutic proposal from a PopPK model

Helder Duarte(1), Ana Mirco(2), Paulo Paixão(1), José A.G. Morais(1), Fátima Falcão(2), Nuno Silva(1)
(1) Faculdade de Farmácia da Universidade de Lisboa, Lisboa, Portugal (2) Centro Hospitalar Lisboa Ocidental, Lisboa, Portugal

Objectives: To develop a population pharmacokinetic model of amikacin in premature newborns babies. From the estimated population model, establish new therapeutic protocol for initial therapy.

Methods: The population pharmacokinetic model was developed from retrospectively collected data of 90 premature newborn babies, with a total of 302 individual concentration-time points, using a nonlinear mixed effects model with Monolix® software(1). Demographic, clinical and analytic data were used to explain between subject variability on each PK parameter. Simulations from the developed popPK model were conducted in order to evaluate the current therapeutic protocol in the clinical setup, as well as to improve the achievement of the therapeutic goals.

Results: Pharmacokinetic profile of amikacin after short term IV infusion was adequately described with a one compartment model with first order elimination and an additive and proportional residual error model. Body weight was identified as predictive of both volume of distribution and serum clearance. Creatinine clearance, post menstrual age and the need of parenteral nutrition were also identified as predictive of individual clearance. In the final model, volume was estimated as 32.7 (L/70 kg). Clearance was estimated as 2.07 (L/h/70kg) for patients without parenteral nutrition and 1.52 (L/h/70 kg) for those with parenteral nutrition needs. These figures are consistent with current literature(2). Unexplained between subject variability was 37.6% for volume and 36.9% for clearance. Residual variability was 0.335 mg/L with a proportional component of 35.4%. Evaluation through simulations of the currently implemented therapeutic protocol in the clinical setup showed that more than 50% of the patients had the potential to present either sub therapeutic or toxic peak concentrations. New recommendations improved the percentage of peak concentrations within therapeutic goal to more than 65%, without worsening of the expected trough concentrations.

Conclusions: Our final popPK model showed a 40% and 50% reduction of unexplained inter-individual variability on volume and clearance respectively. New initial therapeutic recommendations were able to improve, from ca. 40% to ca. 60% the number of peak plasma concentrations within therapeutic target. An easily readable table based on the new recommendations is proposed for clinical use.

References:
[1] Lavielle M, Mentré F. Estimation of Population Pharmacokinetic Parameters of Saquinavir in HIV Patients with the MONOLIX Software. J Pharmacokinet Pharmacodyn [Internet]. 2007 Mar 30;34(2):229–49. Available from: http://link.springer.com/10.1007/s10928-006-9043-z
[2] Murphy J. Aminoglycosides. Clinical Pharmacokinetics: Pocket Reference. 1993. p.1-20

II-77: *Vincent Dubois* Joint modelling of pain intensity and informative dropout in moderate to severe chronic pain patients

Shaonan Wang (1), Chiara Piana (1), Vincent Dubois (1), Muriel Boulton (1), Roberta Bursi (1)
(1) Grünenthal GmbH, Aachen, Germany

Objectives: The aim of this study was to explore joint modelling of pain intensity and informative dropout data from escalating doses of a reference drug and placebo in patients with moderate to severe chronic pain.

Methods: Nonlinear mixed effect modelling (NONMEM) was used to describe exposures of the reference drug and their relationship to average daily pain intensity measured using Numerical Rating Scale change from baseline (NRS_{CHB}). A linear correlation between NRS_{CHB} and probability of dropout was introduced into a time to event model in order to link efficacy and time to dropout [1]. Joint modelling of NRS_{CHB} and dropout was simultaneously performed using NONMEM 7.2. Posterior predictive check (PPC) for NRS_{CHB} was generated by simultaneously simulating NRS_{CHB} and time to dropout. Once a subject was simulated to reach the time to dropout, no further NRS_{CHB} was simulated in that subject

Results: A concentration-NRS_{CHB} relationship was identified for the reference drug and was best described by an E_{max} function. A Weibull model was used to describe the probability of dropout, where the hazard function was dependent on treatment, titration and subject visit time. The PPC for NRS_{CHB} obtained from the joint model with informative dropout showed a better fitting to observations compared to the PPC obtained from the NRS_{CHB} model alone without dropout.

Conclusions: A joint model of NRS_{CHB} and time to dropout was developed and adequately described the observed NRS_{CHB} and Kaplan-Meier curve. By assuming an E_{max} exposure-NRS_{CHB} relationship and by taking into account informative dropout, the joint model was capable of providing a realistic prediction of this trial as well as an opportunity to simulate future trials.

References:
[1] Bjornsson, M.A. et al, Br J Clin Pharmacol 71:6, 899-906

III-01: *Giulia Lestini* Model-based optimal robust design in pharmacometrics

Giulia Lestini, Sebastian Ueckert, France Mentré
IAME, UMR 1137, INSERM, University Paris Diderot, Paris, France

Objectives: Optimal design requires prior information on models and parameters, which may be difficult to guess. Robust design approaches have been developed for taking into account the uncertainty of parameters [1,2]. Our aims were i) to compare various robust design criteria for design in nonlinear mixed effect models (NLMEM) for a PKPD example with continuous data; ii) to evaluate robust designs using a new method for the evaluation of the Fisher information matrix (FIM) for a NLMEM with discrete data.

Methods: The PKPD model was already used for evaluation of adaptive design [3]. We studied robust design assuming prior distributions for two PD parameters k_{out} and IC_{50}, keeping the PK fixed as in [3]. For 50 patients, 3 sampling times were optimized using D-optimality and the following robust criteria: ED (Expectation of Determinant of FIM), EID (Expectation of the Inverse Determinant), ELD (Expectation of log Determinant), and max-min (minimum of determinant). Predicted relative standard errors (pRSE) for 1000 simulated set of parameters were used for designs comparison.

A logistic model for repeated binary response [4] was defined with treatment increasing the slope of the logit of the response with time. Design evaluation was performed using a new method to compute FIM based on Adaptive Gaussian Quadrature and Quasi Random Monte Carlo[5,6]. We evaluated an equispaced design (ξ_{ES}) of 4 sampling times, with 50 patients per arm. We then optimized the two intermediate times (fixing the first and the last) using standard D-optimality (ξ_D) or using the robust ELD criterion (ξ_{ELD}) with prior uncertainties on the slope and treatment effect

Results: For the PKPD example, the different robust criteria led to different optimal designs. ξ_{ELD} performed the best in terms of pRSE across the 1000 simulations, the worst was $\xi_{max\text{-}min}$. For IC_{50} the 90% percentiles for pRSE were 26% for ξ_{ELD} and 64% for $\xi_{max\text{-}min}$.

The evaluation of FIM with the new approach is rather fast, allowing for the first time robust design optimization for discrete longitudinal models. ξ_D and ξ_{ELD} were very close. ξ_{ES} has a loss of efficiency of 0.82 compare to ξ_D. When prior uncertainty is assumed, the loss of efficiency is 0.66 compared to ξ_{ELD}.

Conclusions: Robust designs criteria showed better performance of ξ_{ELD} in NLMEM. Robust and optimal designs are also useful in the context of binary response studies, providing better results than equispaced design.

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

References:
[1] Dodds MG, Hooker AC, Vicini P. Robust population pharmacokinetic experiment design. J Pharmacokinet Pharmacodyn. 2005 Feb;32(1):33–64.
[2] Foo L-K, Duffull S. Methods of Robust Design of Nonlinear Models with an Application to Pharmacokinetics. J Biopharm Stat. 2010 May 19;20(4):886–902.
[3] Lestini G, Dumont C, Mentré F. Influence of the Size of Cohorts in Adaptive Design for Nonlinear Mixed Effects Models: An Evaluation by Simulation for a Pharmacokinetic and Pharmacodynamic Model for a Biomarker in Oncology. Pharm Res. 2015 Oct;32(10):3159–69.

[4] Ogungbenro K, Aarons L. Population Fisher information matrix and optimal design of discrete data responses in population pharmacodynamic experiments. J Pharmacokinet Pharmacodyn. 2011 Aug;38(4):449–69.
[5] Ueckert S, Mentré F. Computation of the Fisher information matrix for discrete nonlinear mixed effect models. 8th International Conference of the ERCIM WG on Computational and Methodological Statistics (CMStatistics) University of London, UK. 2015.
[6] Ueckert S, Mentré F. Computation of the Fisher information matrix for discrete non-linear mixed effect models. Population Optimum Design of Experiments (PODE) Isaac Newton Institute for Mathematical Sciences, Cambridge. 2015.

III-02: *Lia Liefaard* Mixed effects modelling of dose-response cough count data

Lia Liefaard (1)
(1) GlaxoSmithKline, Stevenage, United Kingdom

Objectives: To analyse dose-response count data from two cough challenging compounds, citric acid (CA) and capsaicin (Caps), and to quantify the effect of GSK2339345 on the dose-response relationships, using mixed effects analysis.

Methods: The cough challenge test consisted of subjects receiving increasing doses of CA (2-fold increments; 0.03-4M) or Caps (2-fold increments; 0.49-1000uM), and counting of coughs for 30 seconds following each dose. The effect of GSK2339345 was tested by performing the tests after administration of GSK2339345 or placebo (A/P) in each subject in randomised order [1, 2]. The resulting dose-response datasets had data from 9/9 (A/P) subjects for CA, and from 11/10 (A/P) subjects for Caps.

The dose-response profiles of CA and Caps were analysed by NLME modelling using NONMEM 7.2.0 [3]. The relationship between CA or Caps dose and number of coughs was modelled using an Emax function (gamma fixed to 1). The effect of treatment with GSK2339345 was investigated by implementing proportional differences between A/P in Emax and ED50. Between-subject variability (BSV) was tested as exponential error on model parameters. Poisson and Negative Binomial (NB) distributions were investigated. Model development was guided by log likelihood ratio test (-2LL) and exploratory and diagnostic plots as presented by Zamuner et al [4].

Results: For all models tested (with/without BSV/treatment effect) the NB distr models performed better than Poisson for both CA and Caps. Interestingly, implementing a treatment difference between GSK2339345 and placebo in ED50 for CA or in EMAX for Caps significantly improved the fit for Poisson, but not for NB distr models. The NB distr models *without* treatment effect had lower Obj F than the Poisson distr models *with* treatment effect, suggesting there was no real treatment effect, but rather, in the Poisson distr models it described variability within a subject. The exploratory and diagnostic plots showed little difference in the dose-response curves for CA and Caps between A/P, confirming that any treatment effect will be small.

Conclusions: Even if only data from 9-11 subjects were available, the dose-response count data with CA and Caps could be described by an Emax model with Poisson or NB distributions. A small treatment effect of GSK2339345 was identified in the Poisson, but not in the NB distr models; this was likely because of variability within subjects.

Sponsored by GSK (study 117720)

References:

[1] Hilton EC, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modelling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. J Allergy Clin Immunol (2013) 132:847-55.
[2] Badri H, Satia I, McGarvey L, MarksKonczalik J, Murdoch RD, Cheesbrough A, Warren F, Siederer S, Smith JA. A randomised, double-blind (sponsorunblind), placebo controlled, cross-over study to investigate the efficacy, effect on cough reflex sensitivity, safety, tolerability and pharmacokinetics of inhaled GSK2339345 in patients with chronic idiopathic cough using an aqueous droplet inhaler. British Thoracic Society Winter

Meeting (2015) P238.
[3] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.
[4] Zamuner S, Sahota T, Liefaard L. Modelling development for count data: NONMEM vs R. PAGE 24 (2015) Abstr 3629 [www.page-meeting.org/?abstract=3629].

III-03: *Andreas Lindauer* Time-to-seizure modeling of the antiepileptic drug lacosamide used in monotherapy

Andreas Lindauer (1), Christian Laveille (1), Armel Stockis (2)
(1) SGS Exprimo NV, Mechelen, Belgium; (2) UCB, Braine-l'Alleud, Belgium

Objectives: To quantify the relationship between exposure to lacosamide (LCM) and seizure probability in monotherapy and to explore the relationship with other covariates, including age and disease severity. To perform simulations exploring the effect of changes to the dosing regimen of LCM on the clinical endpoint.

Methods: A structural time-to-event model for dropouts and seizures was developed using data from a study (N01061) testing levetiracetam and carbamazepine controlled-release (CBZ-CR). Subsequently, the model was updated with data from a recently completed trial (SP0993) comparing LCM to CBZ-CR. Trough plasma concentrations of LCM were analyzed with a previously developed population PK model. Individual PK parameter estimates were used to derive the daily AUC. Final PK, dropout/seizure models for LCM were used for simulations assessing the impact of changes to the dosing regimen.

Results: Data from 883 patients in SP0993 were used for modeling. A time-to-event model was developed describing the time-varying hazard of dropout using step-functions. Patients in the LCM group had a slightly lower risk of dropping out compared to those receiving CBZ-CR.

The repeated time-to-seizure data were best described by a Weibull distribution with parameters estimated independently for the first and for subsequent events [1]. Daily AUC was linearly related to the log-hazard. Disease severity, expressed as the number of seizures a patient experienced in the 3 months prior to the study (NSP3M), was found to be a strong predictor of seizure-probability with about 2.6-fold (90% CI: 2.01 – 3.31) higher risk of seizures for patients with 7 to 50 NSP3M compared to the reference category (NSP3M: 2-6). In the LCM group the hazard ratio of a first seizure for a patient aged 65 compared to 41 years (median) was 0.74 (90% CI: 0.59 – 0.88).

Simulations suggest that an individualized dosing regimen for LCM, with an initial target dose of 400 mg/day for patients with NSP3M>7, could potentially result in about 8% more patients seizure-free for 6 months at the last evaluated dose level compared with an initial target dose of 200 mg/day.

Conclusions: Baseline disease severity (NSP3M) was the most important predictor of the seizure probability in the study. Simulations suggest that dose individualization based on NSP3M could potentially be beneficial for patients with more than 7 seizures in the past 3 months. Clinical data are needed to confirm these simulation findings.

UCB-sponsored

References:
[1] Abrantes J, Almeida A, Sales F, Falcao A, Jönsson S. A repeated time-to-event model for epileptic seizures in patients undergoing antiepileptic drug withdrawal during Video-EEG monitoring. PAGE-meeting 2014, Alicante. http://www.page-meeting.org/?abstract=3180

III-04: *Ling Xue* Theory based PK-PD of S- and R-warfarin: influence of body size, composition and genotype

Ling Xue (1), Nick Holford (2), Liyan Miao (1)
(1) Department of Clinical Pharmacology, The First Affiliated Hospital of Soochow University, Suzhou, China
(2) Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Objectives: 1) Apply a theory based mechanistic model to describe the PK and PD of S- and R-warfarin [1] 2) To explore the effect of body size, body composition [2] and genotype on warfarin PKPD parameters.

Methods: Blood samples for S- and R-warfarin were taken in addition to measurement of INR from 264 patients. Total (bound plus unbound) concentrations were measured by UPLC/MS-MS. Genotypes were measured using pyrosequencing of DNA extracted from blood leukocytes. A sequential population PK parameter with data method was used to describe INR. The PKPD model assumed an immediate effect on the turnover of prothrombin complex activity (PCA). INR was assumed to be equal to 1/PCA. Data were analyzed using NONMEM.

Results: The warfarin PK model had first-order input, one compartment distribution and first-order elimination. The input was assumed to be the same for both enantiomers with enantiomer specific estimates for CL and V. Theory based allometry and normal fat mass described size associated differences. CYP2C9 *1/*3 genotype had CL reduced for S- compared with *1/*1, but increased for R-warfarin. Bootstrap statistics for CL and V for each enantiomer are shown in Table 1.

Table 1 Warfarin pharmacokinetic parameters

Parameters	Mean	2.5%	97.5%	RSE (%)
CLS L/h	0.234	0.197	0.272	11
VS L	25.40	22.40	28.41	6
CLR L/h	0.141	0.120	0.155	12
VR L	16.99	15.04	18.90	6
FCYP2C9 *1/*3 CLS	0.818	0.652	0.975	11
FCYP2C9 *1/*3 CLR	1.220	1.025	1.401	8
RUVS prop	0.263	0.247	0.277	3
RUVS add mg/L	0.005	0.002	0.008	27
RUVR prop	0.230	0.217	0.241	3
RUVR add mcg/L	0.000	0.000	0.000	0

A sigmoid Emax PD model inhibiting PCA synthesis best predicted INR as a function of S-warfarin concentration. R-warfarin effects were small and best described by competitive antagonism of S-warfarin. VKORC1 AA and CYP4F2 CC or CT genotype had lower C50 for S-warfarin. Bootstrap statistics for the potency of S-warfarin (C50S) and R-warfarin (IC50R) and the turnover half-life of PCA (T2PCA) are shown in Table 2.

Table 2 Warfarin PKPD and turnover parameters

Parameters	Mean	2.5%	97.5%	RSE (%)
C50S mg/L	0.386	0.261	0.552	21
HILL	2.53	2.08	3.04	10
T2PCA h	12.2	11.0	13.6	46
IC50R mg/L	21.8	0.92	198	257
FVKORC1 AA C50	0.719	0.605	0.806	7
FCYP4F2 CC C50	0.767	0.637	0.869	8
FCYP4F2 CT C50	0.761	0.649	0.881	8
RUV prop	0.180	0.168	0.191	3

Conclusions: A theory based PKPD model described warfarin concentrations and clinical response. Expected genotype effects were confirmed. The role of body composition as a determinant of PK parameters was identified. R-warfarin behaves more like a competitive antagonist of S-warfarin than a less potent inhibitor of PCA synthesis.

References:

[1] Holford NH. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. Clin Pharmacokinet. 1986; 11(6):483-504.
[2] Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009; 24(1):25-36.

III-05: *Jesmin Lohy Das* Population pharmacokinetic and pharmacodynamic (PK/PD) modelling of emerging artemisinin resistance in Southern Myanmar

Jesmin Permala(1), Myat P. Kyaw(2), Myat H. Nyunt(2), Khin Chit(2), Moe M. Aye(2), Kyin H. Aye(2), Mats O. Karlsson(1), Martin Bergstrand(1), JoelTarning (3,4).

(1)Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (2) Department of Medical Research (Lower Myanmar), Yangon, The Republic of the Union of Myanmar. (3) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. (4) Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, UK.

Objectives: Malaria still kills almost 2,000 people each day, mainly children under the age of five. The artemisinin compounds are the most effective antimalarial drugs for uncomplicated and severe *Plasmodium falciparum* malaria. However, artemisinin resistance has been confirmed in the Mekong sub-region of Southeast Asia (1), threatining our ability to control and eliminate malaria. The aim of this work was to evaluate the PK/PD properties of artesunate (ARS) and its active metabolite, dihydroartemisinin (DHA), in patients with sensitive and resistant *falciparum* malaria infections to confirm the reach of artemisinin resistance to Southern Myanmar.

Methods: Fifty (50) subjects were recruited and received daily oral artesunate monotherapy (4 mg/kg) (2). Frequent plasma samples up to 8 hours post-dose and parasite microscopy counts every 12 hours until 2 consecutive negative readings were obtained. Data were evaluated using nonlinear mixed-effects modelling. Drug concentrations (PK) below the LOQ were characterized using the M3 method, whereas parasite counts (PD) below the LOQ were omitted.

Results: The absorption of artesunate was best characterized by a flexible transit-compartment (n=3) model, followed by one-compartment disposition models for artesunate and dihydroartemisinin. The only significant covariate effect was body weight, implemented as a fixed allometric function on clearance and volume parameters for both artesunate and dihydroartemisinin. Relative bioavailability was fixed to unity for the typical subject to allow between-subject variability in the same parameter. The population parameter estimates for both parent and metabolite (CI, %RSE), were CL_{ARS}/F 848 L/h (739-933, 6.4%), CL_{DHA}/F 36.8 (32.6-40.8, 6.2%), V_{ARS}/F 640L (497-789, 12.6%), V_{DHA}/F 49.5L (42-56.5, 8.1.

The drug-dependent parasite killing effect of dihydroartemisinin was implemented using an E_{max} function, with a mixture model discriminating between sensitive and resistant parasites. EC_{50} was fixed to 30 nM (prior information from a similar study) due to the inability to estimate this parameter reliably (3). Overall 70% of the studied population was estimated to have resistant infections. Inter-individual variability in E_{max} was estimated for the resistant population but not retained in the sensitive population

Conclusion: In conclusion, the PK/PD properties of artesunate and its active metabolite, dihydroartemisinin, were well characterized and a mixture model was successfully implemented to differentiate between drug sensitive and resistant parasites in this population.

References:

[1] World Health Organization. Guidelines for the treatment of Malaria. 2015;3rd Edition.
[2] Kyaw M.P., Nyunt M.H., Chit K., Aye M.M., Aye K.H., Aye M.M., Lindegardh N., Tarning J., Imwong M., Jacob C.G., Rasmussen C., Perin J., Ringwald P., Nyunt M.M. Reduced Susceptibility of Plasmodium falciparum to Artesunate in Southern Myanmar. PLoS One. 2013;8(3):e57689.

[3] Das J.P.L. Population Pharmacokinetic-Pharmacodynamic (PK/PD) Modelling of Emerging Artemisinin Resistance in Southeast Asia. Oral presentation. ICAAC. 2015.

III-06: *Kurt Long* Identification of causal pathways determining the relationship between pathogen-specific infection and impaired growth among children < 59 months in Mirzapur, Bangladesh

Kurt Z. Long (1), Salvador Zamora (2), Inong Gunanti (1), Georgina Mora (3), Matthew M. Hutmacher (4), Policy Delivery and Implementation Surge Team - representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community.

(1) Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland, (2) Mathematics Department, National University of Mexico, DF, Mexico, (3) Program in Nutrition of Childhood and Adolescence, Secretariat of Health, Xalapa, Veracruz, Mexico, (4) Ann Arbor Pharmacometrics Group, Ann Arbor, Michigan, USA

Objectives: The burden of childhood diarrhea and malnutrition remains high in South Asia due to inadequate household sanitation, lack of access to improved water and poor hygiene practices [1]. We addressed the relationship between household factors, enteric pathogen infections (EPI) and impaired growth among children residing in rural communities of Bangladesh.

Methods: The relationship between household factors, EPI and impaired growth was evaluated using data from the Global Enteric Multicenter Study site of Mirzapur, Bangladesh [2]. Stool specimens collected at enrollment from children with moderate-to-severe diarrhea and matched controls were screened for bacterial, viral and protozoa EPI. Height measurements of children were also taken and information on sanitation facilities, water sources, household animals, cooking fuel type, caretaker education and hand washing practices were collected. Structural equation models tested pathways directly linking household factors with stunting (< - 2 height-age-Z score) or indirectly through their effects on EPI transmission. Effects of handwashing behaviors, water sources and caretaker education were also tested directly and indirectly.

Results: *Giardia lamblia* and *Cryptosporidium* infections were associated with increased stunting among older children. Dog or goats in compound were directly associated with increased stunting while having a refrigerator or non-dirt floor was associated with reduced stunting. Cow dung fuel use when caretakers reported no handwashing before eating had an indirect effect due to increased prevalence of *Cryptosporidium*. A traditional latrine with caretakers reporting no handwashing before cooking was also associated with increased prevalence of *G. lamblia* and *Cryptosporidium* infections.
Increased *Cryptosporidium* was associated with child feces disposal when caretaker had no formal education. Greater caretaker education was directly associated with reduced stunting and indirectly through an effect on on *Cryptosporidium*. Overall, caretaker education had the greatest beneficial effect on stunting through direct and indirect pathways.

Conclusions: Causal pathways of childhood stunting were identified that involved animal and environmental factors as well as distinct hygiene-related behaviors. These results can inform the design. implementation and evaluation of different interventions to more effectively reduce diarrhea burden and stunting.

References:

[1] Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 2008;371:243-60.
[2]. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology

of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet. 2013;382:209-22.

III-07: *Dominik Lott* Population pharmacokinetics of the selective S1P1 receptor modulator ponesimod

Dominik Lott (1,2), Jasper Dingemanse (1), Thorsten Lehr (2), Andreas Krause (1)
(1) Actelion Pharmaceuticals Ltd, Department of Clinical Pharmacology, Modeling and Simulation, Allschwil, Switzerland, (2) Saarland University, Department of Clinical Pharmacy, Saarbrücken, Germany

Objectives: Development of a population pharmacokinetic (PK) model for the characterization of the reversible, orally active, selective $S1P_1$ receptor modulator ponesimod, including the influence of different formulations (capsule, tablet), disease (psoriasis, multiple sclerosis, hepatic impairment), and demographics (body weight, age, race).

Methods: Plasma concentration-time data from 680 individuals in 13 clinical studies were pooled. The data set comprises single doses up to 75 mg, multiple once-daily doses up to 100 mg as well as different up-titration regimens. In total, 13700 ponesimod concentration measurements were available.

Different structural models, i.e., 1-, 2-, and 3-compartment models with different absorption models were assessed. Following the selection of the structural model, the influence of covariates was assessed by using forward inclusion-backward deletion. The adequacy of the model was evaluated based on visual predictive checks, goodness-of-fit plots, and parameter variability.

Results: The PK characteristics of ponesimod were accurately described by a two-compartment model with sequential zero/first-order absorption, inter-compartmental drug flow (Q/F=21 L/h), and linear apparent clearance (CL/F=6.6 L/h). The estimated apparent volumes of distribution were 165 L and 107 L for the central the peripheral compartment, respectively.

Higher body weights (100 kg), psoriasis, and multiple sclerosis were identified to significantly increase the central volume of distribution by 28%, 45%, and 21%, respectively. Clearance was significantly lower in subjects with mild (-30%), moderate (-52%), and severe (-68%) hepatic impairment, subjects of race 'Black' (-15%), and affected by body weight (higher clearance with increased body weight).

The impact of the identified covariates on ponesimod steady-state exposure largely lies within the margins of the inter-subject variability with the exception of hepatic impairment. Increases of up to 212% were predicted for severe cases of liver dysfunction.

Conclusions: The analysis shows that the inter-individual variability in the PK of ponesimod can partially be explained by covariates that were identified as statistically significant. However, the net effect on steady-state exposure is small and considered as not clinically relevant with the exception of hepatic impairment.

The diversity of the underlying data, the inclusion of a large variety of studies as well as the number of concentration measurements included make this analysis a robust and valuable tool to support dosing strategies for ponesimod.

III-08: *Gaohua Lu* A Novel Mechanistic Approach to Predict the Steady State Volume of Distribution (Vss) using the Fick-Nernst-Planck Equation

Lu Gaohua, David B. Turner, Ciaran Fisher, Ariane Emami Riedmaier, Helen Musther, Iain Gardner and Masoud Jamei
Simcyp Limited (a Certara Company)

Objectives: The notion that unbound, unionized drug concentrations are in equilibrium between intracellular and extracellular water at steady state is a key assumption of some *in silico* methods for predicting tissue:plasma ratio (kp) and volume of distribution at steady state (Vss) [1, 2], Mathematically this is expressed as Kpuu,uu = 1. However, there is evidence that ionised drug species can also cross membranes (albeit at a lower rate than unionised drug) and that membrane potential and pH differences across membranes could result in Kpuu,uu having values not equal to 1. The Rodgers and Rowland method (R&R) for predicting Kp and Vss [1, 2] has been extended to account for electrolyte passive permeability across cell membranes.

Methods: Membrane potential is incorporated into the physiologically-based pharmacokinetic (PBPK) model [1-3] to account for the passive permeation of both neutral molecules (Fick's law) and ionized molecules (Nernst-Planck equation) across the cell membranes. Kpuu,uu is derived from the steady-state Fick-Nernst-Planck equation. The Kp and Vss prediction algorithm in R&R method is revised to use non-unity values of Kpuu,uu. The new method is tested using a library of compounds (n = 71, including 7 neutral compounds, 35 monoprotic bases, 12 monoprotic acids, 6 diprotic bases and 11 ampholytes). The performance of the new method is compared to the predicted Vss from the R&R method as well as the observed Vss.

Results: Assuming a, physiologically reasonable, membrane potential (-10 mV for red blood cells and -41 mV for tissue cells) and passive permeability for electrolytes (2-4 log-unit lower than neutral molecules), Kpuu,uu > 1 was predicted for basic compounds and Kpuu,uu < 1 for acidic compounds. Compared to the R&R method, the new method predicted higher Vss for basic compounds, but lower Vss for acidic compounds. The new method improved Vss prediction for strong bases (pKa > 7; n = 22). Vss was predicted within 2 or 3 -fold of observed values for 16 and 20 compounds, respectively. In contrast, the classic R&R method predicted Vss within 2 or 3 -fold of observed values for 13 and 17 compounds, respectively.

Conclusions: The results show accounting for electrolyte passive permeation has an impact on the prediction of Vss and the predictions for the strongly basic compounds investigated was improved. Further research is required to investigate the model performance for a bigger dataset.

References:
[1] Rodgers T, Leahy D and Rowland M (2005) Physiologically based pharmacokinetic modelling 1: predicting the tissue distribution of moderate-to-strong bases. J Pharm Sci 94:1259-1276.
[2] Rodgers T and Rowland M (2006) Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. J Pharm Sci 95:1238-1257.
[3] Jamei, M., G. L. Dickinson, et al. (2009). A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: A tale of 'bottom-up' vs 'top-down' recognition of covariates. Drug Metab Pharmacokinet 24(1): 53-75.

III-09: *Sreenath M Krishnan* Population modeling of uni- and three- dimensional and density-based tumor measurements in gastro-intestinal stromal tumor (GIST) patients treated with imatinib

Sreenath M. Krishnan (1), Emilie Schindler (1), Gaia Schiavon (2), Lena E. Friberg (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (2) The Institute of Cancer Research: Royal Cancer Hospital, London, UK.

Objectives: Three-dimensional (3D) and density-based tumor metrics have been suggested to better discriminate tumor response to treatment than the traditional unidimensional (1D) metrics for gastro-intestinal stromal tumor (GIST) which often exhibit non-uniform size changes. This study aims to characterize the longitudinal 1D, 3D and density responses of liver metastases in imatinib-treated GIST patients and quantify the inter-individual (IIV) and inter-lesion variability (ILV).

Methods: Data were obtained from a retrospective, non-interventional study involving 77 GIST patients treated with oral imatinib at a starting dose of 400 mg/800 mg q.d. (74/3) [1]. Maximum trans-axial diameter (MTD), software-calculated segmented volume (V_s), calculated ellipsoidal volume (V_e) and density data were collected from 137 lesions (1-2 per patient) at baseline and at least one post-baseline visit with median follow-up time of 360 days. Tumor growth inhibition (TGI) models with constant, exponential or Gompertz growth were explored to describe MTD, Vs and Ve data. Indirect response models (IDR) with inhibition of the production or stimulation of the loss of response were investigated for tumor density. IIV and ILV were tested in all parameters. All models were combined into a joint model to explore correlations.

Results: TGI models with an exponential growth and a linear dose-driven drug effect that washes out over time [2] best characterized the MTD, V_s and V_e data. A mixture model described the bimodal distributions of the baseline data and accounted for ILV. The model-predicted doubling time was typically lower for V_e (1.3 years) and V_s (1.5 years) than for MTD (8.7 years). The growth rate constants and drug effect parameters were associated with large IIV but no ILV. An IDR model with stimulation of the loss of response adequately described tumor density data. Large IIV (120 %CV) and ILV (53 %CV) were identified in the drug effect. High correlations (>99%) were estimated between MTD, V_s and V_e model parameters. Correlations between the density model parameters and MTD, V_s and V_e model parameters were low (<20%).

Conclusions: The developed models adequately described the longitudinal 1D, 3D and density data of liver metastases in imatinib-treated GIST patients. All tumor responses were associated with large IIV. ILV was identified in the drug sensitivity of density only. In a next step, the model-predicted tumor metrics will be evaluated as predictors of overall survival.

Acknowledgements: This work was supported by the Swedish Cancer Society.

References:

[1] Schiavon G. et al. Eur J Cancer (2014) 50:972-80.
[2] Claret et al. J Clin Oncol (2009) 27: 4103-4108.

III-10: *Vincent Madelain* Favipiravir pharmacokinetics in non-human primates: insights for future efficacy studies against hemorrhagic fever viruses

Vincent Madelain (1), Jérémie Guedj (1), France Mentré (1), Thi Huyen Tram Nguyen (1), Koichi Yamada (2), Yousuke Furuta (2), Takumi Kadota (2), Anne-Marie Taburet (3), Frédéric Jacquot (4), Xavier de Lamballerie (5,6), Hervé Raoul (4)

(1) INSERM, IAME, UMR 1137, F-75018 Paris, France ; Université Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, F-75018 Paris, France (2) Dept.,Research Laboratory of Toyama Chemical Co., Ltd, Japan (3) Hospital Bicêtre, Assistance Publique-Hôpitaux de Paris, DHU Hepatinov ; INSERM U1184, Center for Immunology of Viral Infections and Autoimmune Diseases, Université Paris-Sud, Kremlin Bicêtre, France (4) Laboratoire P4 Inserm-Jean Mérieux, US003 Inserm, 69365 Lyon, France (5) Aix Marseille Université, IRD French Institute of Research for Development, EHESP French School of Public Health, EPV UMR_D 190

Objectives: Favipiravir is an antiviral nucleotide analogue with exhibited antiviral effectiveness against several hemorrhagic fever viruses in small animals [1–3], but its efficacy in non-human primates (NHPs) has not been assessed. Here, in order to prepare efficacy studies, we characterize for the first time the pharmacokinetics (PK) of favipiravir administered intravenously for up to 2 weeks.

Methods: PK studies of favipiravir in Cynomolgus macaques from Chinese and Mauritian origin were performed in Japan and France, respectively. Favipiravir was given up to 14 days, with a loading dose of 200-250 mg/kg BID at day 1 followed by a maintenance dose of 60, 100 or 150 mg/kg BID (Chinese NHPs) and 100, 150 or 180 mg/kg BID (Mauritian NHPs). Following a population approach, a PK model was developed to estimate the effect of dose, sex, breed, and to predict by simulation the exposure achieved in various dosing regimen. Assuming a protein binding rate of 50% [4], we proposed doses of favipiravir needed to achieve free concentrations close or above EC_{50} values reported for Ebola virus (50 µg/L [5]), Rift Valley fever and Lassa viruses (5 µg/L [1,3]) and for Crimea-Congo virus (1 µg/L [6]).

Results: No serious abnormality in the 30 NHPs studied was observed at any of the doses tested. PK was highly non-linear over doses and time with a 20-50% reduction in average concentration at day 14 compared to day 7. This non-linearity was explained in the model by a time-dependent elimination mediated by aldehyde oxidase, the main enzyme involved in favipiravir metabolism [7]. The clearance rate was also affected by breed, with concentrations much lower in Mauritian than in Chinese NHPs. Consequently doses of 150 and 130 mg/kg BID in NHPs of Mauritian and Chinese origin, respectively, may be needed to maintain concentration above or close to favipiravir's EC_{50} against EBOV until day 14. Lower maintenance doses of 130 and 100 mg/kg BID in NHPs of Mauritian and Chinese origin, respectively, should be sufficient for Rift valley fever, Lassa and Crimea-Congo viruses.

Conclusions: Our results shows that favipiravir PK was largely nonlinear over doses and time, leading to a large decrease in concentrations after day 7, that could be captured by a mechanistic enzyme based model. In absence of intracellular data, dose recommendation was based on protein unbound plasma concentrations, but the relevance of this approach will need further efficacy studies.

References:

[1] Oestereich L, Rieger T, Lüdtke A, Ruibal P, Wurr S, Pallasch E, et al. Efficacy of Favipiravir Alone and in Combination With Ribavirin in a Lethal, Immunocompetent Mouse Model of Lassa Fever. J. Infect. Dis. 2015;

[2] Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced

Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res. 2014;105:17–21.
[3] Gowen BB, Wong M-H, Jung K-H, Sanders AB, Mendenhall M, Bailey KW, et al. In vitro and in vivo activities of T-705 against arenavirus and bunyavirus infections. Antimicrob. Agents Chemother. 2007;51:3168–76.
[4] Mentré F, Taburet A-M, Guedj J, Anglaret X, Keïta S, de Lamballerie X, et al. Dose regimen of favipiravir for Ebola virus disease. Lancet Infect. Dis. 2015;15:150–1.
[5] Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. Antiviral Res. 2014;104:153–5.
[6] Oestereich L, Rieger T, Neumann M, Bernreuther C, Lehmann M, Krasemann S, et al. Evaluation of antiviral efficacy of ribavirin, arbidol, and T-705 (favipiravir) in a mouse model for Crimean-Congo hemorrhagic fever. PLoS Negl. Trop. Dis. 2014;8:e2804.
[7] Madelain V, Nguyen THT, Olivo A, de Lamballerie X, Guedj J, Taburet A-M, et al. Ebola Virus Infection: Review of the Pharmacokinetic and Pharmacodynamic Properties of Drugs Considered for Testing in Human Efficacy Trials. Clin. Pharmacokinet. 2016; in press

III-11: *Mats Magnusson* Population PKPD Analysis of CD4 and ACR Response after SC Administration of Tregalizumab to Patients with Rheumatoid Arthritis

Mats O. Magnusson (1), Elodie L. Plan (1), Angela Remy (2), Martin König (2), Silke Aigner (2), Veit Braun (2), Daniela Zipp (2), Xuefei Zhou (2), Ralf Wolter (2), Jörg Schüttrumpf (2), Andrea Wartenberg-Demand (2), Benjamin Dälken (2), Faiza Rharbaoui (2
(1) Pharmetheus, Uppsala, Sweden; (2) Biotest, Dreieich, Germany

Objectives: Tregalizumab (BT-061) is a non-depleting anti-CD4 antibody with antagonist effect on effector T cells and agonist effect on regulatory T cells. Upon completion of the latest phase IIb trial with tregalizumab, Study 986, in rheumatoid arthritis (RA) patients with an inadequate response to methotrexate, a modeling analysis was performed. The aim was to describe the relationship between tregalizumab exposure, or dose, and the response in modulation of cell surface CD4 expression, as well as in clinical efficacy endpoints (American College of Rheumatology [ACR]).

Methods: This population PKPD analysis was based on data from 4 phase II clinical trials with tregalizumab in RA patients (studies 962, 971, 979 and 986). The PK properties of tregalizumab following single and multiple intravenous (IV) and subcutaneous (SC) administrations were first characterized using data from 4 other phase I and phase II studies in healthy volunteers and psoriasis patients (961, 967, 973 and 985). The final PK model was based on 697 samples from 159 subjects. The PK model was used to derive individual PK profiles for all subjects. The data set used in the population PKPD analysis consisted of 3848 CD4 measurements from 489 subjects, and 3726 ACR measurements from 530 subjects. The analysis was performed using non-linear mixed-effects modeling implemented in NONMEM 7.3.0.

Results: The final CD4 model was a direct effect model, where a maximum effect (Emax) function described the relationship between the tregalizumab dose and the inhibitory effect on CD4. The typical CD4 reduction was estimated to 52% in the 200 mg dose group. The final ACR model was a direct study-specific effect model between tregalizumab dose and the discrete probabilities of transition from a responder Markov state to another amongst: non-responder, ACR20, ACR50 or ACR70. In comparison to placebo effect (methotrexate only) at 12 weeks, the 200 mg dose in study 986 was predicted to lead to an 11% (absolute) reduction in the transitions from ACR20 to non-responder and an increase in the transitions from ACR20 to ACR20, ACR50 and ACR70, of 6%, 5% and 0.5%, respectively.

Conclusions: The tregalizumab dose-CD4 relationship, as well as the tregalizumab dose-ACR relationship, in studies 962, 971, 979, and 986 were well captured by the developed PKPD models. The models predicted that at the highest dose level studied, 200 mg, the maximal effect in CD4 was not reached whilst minor ACR improvements were achieved.

III-12: *Adedeji Majekodunmi* Mechanistic modelling of naive CD4+ T cell homeostasis in HIV-infected children on anti-retroviral therapy

Adedeji Majekodunmi (1, 2), Nigel Klein (2), Robin Callard (1,2), Joanna Lewis (3)
(1) CoMPLEX, UCL, (2) Institute of child health, University College London, (3) Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus

Objectives: The overall aim of this work is to develop a differential equations model to facilitate understanding of the changes taking place within the naive CD4+ T cell compartments in HIV-infected children receiving ART. Naive T cell compartments to be considered include recent thymic emigrants and central naive CD4 T cells.

Methods: A total of 223 HIV-infected children receiving ART were included for analysis (median age- 4.7 (IQR: 2.0-9.2)). The dataset consisted of 1738 naïve CD4 counts collected prospectively from the ARROW trial [4] over a median duration of 3.2 yrs (IQR: 3.2-3.3). The total naive CD4 counts were fitted to account for age differences using the exponential functions described in Bains et al [1,2]. A single compartment model of total naive CD4+ T cells was fitted to the dataset and a total of three parameters were estimated using the framework of non-linear mixed effects modelling implemented in the NONMEM software (FOCE with random effects on all three parameters).

Results: Diagnostic plots showed that the single compartment model was a good fit for the data. We found that recent thymic emigrants (RTEs) were mostly responsible for immune reconstitution in children receiving ART whilst the central naive T cells maintained a steady state throughout the initial 3.3 years on ART. Fixed effects estimates obtained include proportion of theoretical thymic (3.55 ± 0.424 cells/day, ETA: 3.83), resultant loss rate (0.295±0.032 cells/day, ETA: 1.8) and initial CD4 count at start of ART (118 ±24.3 cells/µL, ETA: 1.32). As expected, we found that younger children had higher thymic outputs and initial CD4 counts compared to older children. Children with poor recovery of their naïve CD4 count did not demonstrate particularly low thymic outputs.

Conclusions: A mechanistic model can be used to understand naïve CD4 T cell homeostasis in HIV-infected children receiving ART. This model has been fitted without the need for transforming the raw CD4 counts prior to the fit. Recent thymic emigrants are central to CD4 T cell recovery in children receiving ART. Poor naïve CD4 recovery was not explained by low thymic outputs. Thymic output estimate will be improved further by considering addition of an extra viral load loss term into the model. Further work will extend the one-compartment model to a two-compartment model and extensive covariate analysis will be conducted.

References:

[1] Bains I, Antia R, Callard R, Yates AJ. Quantifying the development of the peripheral naive CD4+ T-cell pool in humans. Blood. 2009 May 28; 113(22): 5480-7.
[2] Iren Bains, Rodolphe Thiebaut, Andrew J. Yates and Robin Callard. Quantifying Thymic Export: Combining Models of Naive T cell Proliferation and TCR Excision Circle Dynamics Gives an Explicit Measure of Thymic Output, The Journal of Immunology, 2009; 183; 4329-4336.
[3] Kohler S, Thiel A. Life after the thymus: CD31+ and CD31- human naive CD4+ T-cell subsets. Blood. 2009 Jan 22; 113(4): 769-74.
[4] The ARROW trial team. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial, Lancet. 2013 Apr 20; 381(9875): 1391-403.

III-13: *Victor Mangas-Sanjuan* Exploring Inter-study variability in the context of modeling unperturbed xenograft data

Maria Garcia-Cremades (1), Victor Mangas SanJuan (1), Iñaki F Troconiz (1), Gary Mo (2), Celine Pitou (2), Philip W Iversen (3), Johan E Wallin (2)
(1) Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona, Spain, (2) Global PK/PD & Pharmacometrics, Eli Lilly and Company (3) Lilly Research laboratories, Eli Lilly and Company

Objectives: Pharmacokinetic/Pharmacodynamic characterization of anti-tumor drug effects using xenograft studies [1] is an important process during early stages of oncology drug development. A common feature in those studies is the presence of experimental variability (i. e., same tumor cell lines), and it is not uncommon to note discrepancies in model-related parameters and response outcomes (i.e., % tumor growth inhibition). Proper characterization of different levels of variability (individual and experimental) may facilitate interpretation of individual experiments, as well as optimal design. The objectives of this work are to quantify the extent and the impact of inter-study variability on the model parameters reflecting initial tumor conditions (TS_0) and proliferation rate ($lambda_1$).

Methods: Longitudinal tumor volume data from animals (n=239) that received saline administration were used for this analysis. The selected analysis dataset represent different lung cancer tumor cell lines (n=12). For each type of cell line the number of experiments varied from 1 to 13. All the analyses were performed with NONMEM 7.3. Different structural models were fit to the data to characterize the unperturbed tumor growth kinetics. Once the base population model was selected for each cell line, the study variable was incorporated into the model either as a non-ordered categorical covariate, or as second level of variability through the $LEVEL functionality available in NONMEM 7.3.

Results: The unperturbed tumor growth model proposed by Simeoni et al., provided a fair description of the data in all the twelve different tumor cell lines. Including the study variable as second level of variability was significant ($p<0.001$) in those studies with more than three repeated experiments, and for the two main parameters of the model. The magnitude of the inter-study variability in TS_0 and l_1 was estimated between 20-30% and was in the same range compared to the inter-animal variability (10-42%).

Conclusions: This analysis shows that inter-study variability is present in typical xenograft experiments with a moderate magnitude and can be detected with precision in cases with at least four repeated experiments. Current available tools in Pharmacometrics allow proper handling of study effects beyond the covariate effects. Ongoing research focuses on the role of study effects in the perturbed growth model, and its similarities across different types of cancers.

References:
[1] Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, Germani M, Poggesi I, Rocchetti M. Cancer Research 64: 1094-101.

III-14: *Vikash Mansinghka* BayesDB Marcro Indicator Explorer ensemble models for growth outcome country phenotyping

Vikash Mansinghka
Massachusetts Institute of Technology

Objectives: To make it possible for non-technical HBGD stakeholders to ask and answer empirical questions, such as "What countries are probably comparable to Bangladesh in terms of their expression of malnutrition-related variables at the macro-level?" The underlying goal is to empirically ground HBGD-relevant policy advocacy, initiative design, post-mortem analysis, and public debate. This requires an accessible interface, plus means of addressing data quality, model quality, model comparison, model combination, and collaborative analysis.

Methods: Longitudinal macro data were obtained from the Gapminder Foundation [1], including ~500 variables for ~250 countries, some for over 100 years. The data were analyzed using BayesDB [2], a novel probabilistic programming platform that makes it possible for end users to query the probable implications of the data without needing a conceptual or technical understanding of statistics. Bayesian ensembles of models were built from CrossCat [3], as well as mixed effects modeling and machine learning approaches.

Results: The output forms the basis for the BayesDB Macro Indicator Explorer, a web application that enables end users to browse the Gapminder data through the lens of multivariate "country phenotypes". Users can identify the probable comparable countries for any target country and indicator of interest, and compare results across different modeling approaches.

Conclusions: Depending on the target country and indicator, the inferred set of comparables varies greatly. The ease of use suggests that extending the BayesDB MIE to answer a broader class of questions may be fruitful. The inferred dependencies between variables are not sparse; standard analyses that treat each variable independently may thus be inaccurate.

References:

[1] http://gapminder.org
[2] Mansinghka et al. BayesDB: a probabilistic programming platform for querying the probable implications of data. In review; preprint available at arXiv:1512:05006.
[3] Mansinghka et al. CrossCat: a fully Bayesian nonparametric method for analyzing heterogeneous high-dimensional data. In press at the Journal of Machine Learning Research (2016).

III-15: *Ben Margetts* Modelling Severe Human Cytomegalovirus Infections in an Immunocompromised Paediatric Patient Population

Ben K Margetts (1,2,3), Judith Breuer (2,3), Nigel Klein (2,3), and Joseph F Standing (1,2,3)
(1) UCL CoMPLEX, London, UK, (2) UCL Institute of Child Health, London, UK, (3) Great Ormond Street Hospital NHS Foundation Trust, London, UK

Objectives: To develop a viral kinetic (VK) model of Cytomegalovirus (CMV) that predicts how viral load changes in an individual as the infection responds to antiviral therapy.

Methods: Complete clinical datasets were taken from 335 bone marrow transplant (BMT) patients between January 2010 and December 2014, of whom 86 exhibited a serious active CMV infection following their immunosuppressive treatment regime. A total of 1598 CMV viral load observations for all patients over the time period were included. For each of the patients studied, we had access to clinical history, treatment outcomes, and the results of all clinical tests undertaken. These tests include regular white cell counts, white cell subset counts, full blood counts, and a selection of viral load PCRs. Alongside this rich clinical data, we have access to full drug administration datasets for each patient during their stay at the hospital.

Viral load data was fitted to a viral growth model using NONMEM V7 3.0 [1], a growth inhibition term related to antiviral treatment was incorporated into the VK model alongside a growth limiting V MAX term that scales the rate of viral growth against the maximum amount of virus that is possible within an individual. Viral load was used as the primary predictor of treatment outcome as high viral loads (>1 million copies/mL) are typically associated with higher levels of mortality.

Results: The viral kinetic model was shown to appropriately fit the data from the BMT patients, accurately estimating the viral growth and decay during key moments in the patient's disease progression cycle. Model parameters generated during the estimation were appropriate, given the biological context, with viral doubling time agreeing with the faster ~1.4 day CMV doubling time previously shown in BMT patients with CMV infections [2]. Antiviral efficacy was estimated to be highly variable within the patient population. The model can provide realistic disease trajectory simulations that can be fitted to data from newly infected patients, as they present.

Conclusions: A dynamic VK model has now been developed for CMV. Future work will include a dynamic immune component that scales to an individual's lymphocyte count, and the inclusion of individual antiviral PK information. Following this, the use of rich CMV sequencing data currently being collected from BMT patients may allow us to monitor and predict the emergence of drug resistance, and model its impact on the antiviral efficacy.

References:
[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2013. Icon Development Solutions, Ellicott City, Maryland, USA.
[2] Mueller, Nicolas J. "Cytomegalovirus: Why Viral Dynamics Matter." *EBioMedicine* 2.7 (2015): 631.

III-16: *Amelie Marsot* Population pharmacokinetic model of delta-9-tetrahydrocannabinol (THC) in cannabis occasional smokers

A.Marsot, C. Audebert, L. Attolini, J. Micallef, O. Blin
Service de Pharmacologie Clinique et Pharmacovigilance, AP-HM, Pharmacologie intégrée et interface clinique et industriel, Institut des Neurosciences Timone – AMU-CNRS 7289, Aix Marseille Université, 13385 Marseille

Objectives: Cannabis is the most widely used illegal drug in the world. Delta-9-tetrahydrocannabinol (THC) is the main source of the pharmacological effect. Several studies have been carried out to determine pharmacokinetic parameters of cannabinoids in humans. These studies show significant variability in the described models as the values of the estimated pharmacokinetic parameters. The objective of this study was to develop a population pharmacokinetic model for THC in occasional cannabis smokers.

Methods: Twelve male volunteers (age: 20 to 28 years, body weight: 62.5 to 91.0 kg), tobacco (3-8 cigarette per day) and cannabis occasional smokers were recruited from the local community. Mean cannabis cigarette dose was 500 mg and contained 4% THC (20 mg of THC). After *ad libitum* smoking (maximum 30 min), participants provided 16 blood samples up to 72 h after smoking initiation. Population pharmacokinetic analysis was performed using a non-linear mixed effects model, with NONMEM version 7.3 software (ICON Development Solutions). The R version 3.1.2 software (www.r-project.org) was used for goodness-of-fit diagnostics. Demographic data (age and body weight) and biological data (creatinine, urea, glucose, AST and ALT) were investigated as covariates.

Results: A three-compartment model with first-order elimination fitted the data. The model was parameterized in terms of micro constants (k_{10}, k_{12}, k_{21}, k_{23} and k_{32}) and central volume of distribution (V_1). Body weight demonstrated a correlation with k_{10} and V_1 but did not significantly improve predictions. ALT concentration (6.0 to 45.0 UI/l) demonstrated a statistically significant correlation with k_{10}. The mean values (%Relative Standard Error (RSE)) for k_{10}, k_{12}, k_{21}, k_{23}, k_{32} and V_1 were 0.408 h^{-1} (48.8%), 4.070 h^{-1} (21.4%), 0.022 h^{-1} (27.0%), 1.070 h^{-1} (14.3%), 1.060 h^{-1} (16.7%) and 19.10 L (39.7%), respectively. The interindividual variability (%RSE) of k_{10} and V_1, and residual variability (%RSE) were 49.4% (61.7%), 13.8% (fixed), and 53.9% (7.4%), respectively.

Conclusions: In the present study, we have developed a population pharmacokinetic model able to describe the quantitative relationship between administration of inhaled doses of THC and the observed plasma concentrations after smoking cannabis cigarette. Our study also provided an estimate of parameters variation between individuals. In addition, a linear relationship between ALT concentration and value of k_{10} has been described and request further investigation.

III-17: *Lisa Martial* Population PK model and pharmacokinetic target attainment of micafungin in ICU patients

Martial LC(1,2), ter Heine R(1,2), Schouten JA(3), Hunfeld NG(4), van Leeuwen HJ(5) Verweij PE(6,2) Pickkers P(7), Lempers VJ (1,2), Brüggemann RJ(1,2,8)
(1)Department of Pharmacy, Radboud university medical center, Nijmegen, The Netherlands; (2)The Netherlands Radboud Institute for Health Sciences, Nijmegen, The Netherlands; (3)Department of Intensive Care, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; (4) Erasmus Medical Center, Department of Intensive Care, Rotterdam, The Netherlands; (5)Department of Intensive Care, Rijnstate Hospital, Arnhem, The Netherlands (6) Department of Medical Microbiology, Radboud university medical center, Nijmegen, The Netherlands (7)Department of Intensive Care, Radboud university medical center, Nijmegen, The Netherlands; (8) On behalf of the FANTASTIC consortium.

Objectives: Micafungin (MFG) is used as first line treatment of invasive candidiasis/ candidemia in critically ill (ICU) patients. The pharmacokinetics (PK) of many drugs are altered in this population.[1-3] The PK of MFG have been well studied in a wide population of non-ICU patients but there is only limited knowledge on the causes of PK variability and therapy failure in ICU patients.[3] PK of MFG is correlated with treatment outcome: the ratio of the area under the concentration time curve over the minimal inhibitory concentration (AUC/MIC) of ≥3000 is associated with favorable response (85.1%).[4] The aim of our study was to develop a population PK model to identify sources of PK variability of MFG in ICU patients and guide future dose individualization studies.

Methods:MFG PK data from 20 ICU patients with possible or proven candidemia treated with 100 mg MFG daily were used.[3] Two PK curves with daily trough concentrations were drawn. NONMEM 7.3, PsN, R and Pirana were used for model building. V1 and CL were allometrically scaled to body weight (BW). IIV was tested on all parameters and IOV on clearance (CL) and volume of distribution (V). The model was used to calculate the area under the concentration time curve of the dosing interval ($AUC_{0\text{-}24h}$) and AUC/MIC on day 3 of therapy, using an ECOFF for *C.albicans* (MIC 0.016 mg/L).[5] Precision of the parameter estimates were obtained from the covariance step in NONMEM.

Results: Median(range) age and BW were 68(20-84) years and 77(50-134) kg. 356 observations were available for model building. A 2-compartment first order kinetic model described the data well. CL was 1.1 L/h, Q 0.72 L/h, V1 16.7 L and V2 5.43 L, relative standard errors (RSE) 10, 22 16, and 12% respectively. IIV on CL and V1 were 40% and 69% (coefficient of variation [CV]) with RSE 22 and 48%. The correlation between IIV of CL and IIV of V1 was 48%CV (RSE 33%). IOV on V1 resulted in a significant improvement (δOFV -52.5) and was estimated to be 42%CV.
The median $AUC_{0\text{-}24h}$ on day 3 of therapy was 75 mg*h/L (range 75-160). Median AUC/MIC was 4662 (range 2974-10020).

Conclusions: Higher IIV of CL and V1 was observed compared to non-ICU patients.[5] 95% attained the PTA (based on an ECOFF MIC of 0.016 mg/L).[6] We are currently exploring covariates to further improve the model and explain variability in this population. Next we aim to simulate alternative dose strategies to aid further dose individualization of MFG in critically ill patients.

References:
[1]Martial LC, Brüggemann RJ, Schouten JA, van Leeuwen HJ, van Zanten AR, de Lange DW, Muilwijk EW, Verweij PE, Burger DM, Aarnoutse RE, Pickkers P, Dorlo TPC. Dose Reduction of Caspofungin in Intensive

Care Unit Patients with Child Pugh B Will Result in Suboptimal Exposure.
[2] Lempers VJ, Schouten JA, Hunfeld NG, Colbers A, Leeuwen HJ, Burger DM, Verweij PE, Pickkers P, Brüggemann RJ. Altered Micafungin Pharmacokinetics in Intensive Care Unit Patients. Antimicrob Agents Chemother 59:4403–4409. Clin Pharmacokinet. 2015 Dec 9. [Epub ahead of print]
[3] Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA5 Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL; International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014 Jun;14(6):498-509.
[4]Andes D, Ambrose PG, Hammel JP, van Wart SA, Iyer V, Reynolds DK, Buell DN, Kovanda LL, Bhavnani SM. Use of Pharmacokinetic-Pharmacodynamic Analyses To Optimize Therapy with the Systemic Antifungal Micafungin for Invasive Candidiasis or Candidemia. AAC, May 2011, p. 2113–2121.
[5] EUCAST Antifungal Clinical Breakpoint Table v. 8.0 valid from 2015-11-16. http://www.eucast.org/clinical_breakpoints/ Accessed 29-02-2016.
[6]Hebert MF, Smith HE, Marbury TC, Swan SK, Smith WB, Townsend RW, Buell D, Keirns J, Bekersky I. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. J Clin Pharmacol. 2005 Oct;45(10):1145-52.

III-18: *Emma Martin* Modelling based methods to account for dropout in xenograft experiments

Emma C. Martin (1), Leon Aarons (1), James W.T. Yates (2)
(1) University of Manchester, Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, the University of Manchester, M13 9PT, U.K. (2) AstraZeneca, Innovative Medicines, Oncology, Modelling and Simulation, Li Ka Shing Centre, Robinson Way, Cambridge CB2 0RE, U.K

Purpose: Xenograft studies are commonly used to assess the efficacy of new compounds and characterise their dose response relationship [1]. Analysis often involves comparing the final tumour sizes across dose groups [2]. This can cause bias, as often in xenograft studies a tumour burden limit (TBL) is imposed for ethical reasons [3], leading to the animals with the largest tumours being excluded from the final analysis. This means the average tumour size, particularly in the control group, is underestimated, leading to an underestimate of the treatment effect.

Methods: Four methods to account for dropout due to the TBL are proposed, as outlined below, which use all the available data instead of only final observations. The methods were applied to both a simulated data set, and a real example.

1. Modelling – a tumour growth model was fitted to all available data, ignoring drop out, then population estimates of the response at each dose were used to estimate the dose response curve.
2. Pattern mixture – the mice were treated as belonging to different drop out patterns depending on the day they dropped out of the study [4], missing data was then imputed for each drop out pattern based on models fitted to the patterns which were most similar.
3. Censoring - the M3 method was used [5] which is often applied to data below the limit of quantification. The likelihood for missing values is replaced by the likelihood of the missing value truly being above the tumour burden limit, given that the observation is missing due to drop out.
4. Joint modelling – the tumour growth data and the missing data were jointly modelled through shared random effects. A logistic model was used to model the drop out, with the only covariate being the expected tumour size from the tumour growth model.

Results: All four proposed methods led to an improvement in the estimate of treatment effect in the simulated data. The joint modelling method performed most strongly, with the censoring method also providing a good estimate of the treatment effect, but with higher uncertainty. In the real data example, the dose response estimated using the censoring and joint modelling methods was higher than the very flat curve estimated from average final measurements.

Conclusions: Accounting for dropout using the proposed censoring or joint modelling methods allows the treatment effect to be recovered in studies where it may have been obscured due to dropout caused by the TBL.

References:
[1] Tan, M., et al., Repeated-measures models with constrained parameters for incomplete data in tumour xenograft experiments. Stat Med, 2005. **24**(1): p. 109-19.
[2] Hather, G., et al., Growth rate analysis and efficient experimental design for tumor xenograft studies. Cancer Inform, 2014. **13**(Suppl 4): p. 65-72.
[3] Workman, P., et al., Guidelines for the welfare and use of animals in cancer research. Br J Cancer, 2010.

102(11): p. 1555-77.
[4] Yuen, E., I. Gueorguieva, and L. Aarons, Handling missing data in a duloxetine population pharmacokinetic/pharmacodynamic model - imputation methods and selection models. Pharm Res, 2014. **31**(10): p. 2829-43.
[5] Beal, S.L., Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn, 2001. **28**(5): p. 481-504.

III-19: *Jean-Marie Martinez* Modelling and simulation of alirocumab – Part 1: Population pharmacokinetic analysis using a Michaelis-Menten approximation of the target-mediated drug disposition model

Jean-Marie Martinez (1), Aurélie Brunet (1), Fabrice Hurbin (1), A. Thomas DiCioccio (2), Clémence Rauch (1), Laura Lohan (3) and David Fabre (1)
(1) Sanofi, Montpellier, France, (2) Regeneron, Tarrytown, New York, (3) Faculty of Pharmacy, Montpellier, France

Objectives: Like many monoclonal antibodies (mAbs), the PK of alirocumab (an anti-PCSK9 mAb) is characterised by nonlinear, target-mediated PK (Target-Mediated Drug Disposition, TMDD): the elimination is partly mediated by binding to the target antigen. The Pop PK analysis reported here was developed to characterise the PK profile, identify factors affecting alirocumab PK and to compute individual patients' PK parameters and exposures (i.e. $AUC_{0-\tau}$ and C_{max}).

Methods: From a dataset comprised of ~2800 patients (~13700 concentration-time points), a Michaelis-Menten approximation of the TMDD model was used to estimate PK parameters and exposures. The final model described here is a two-compartment model with a first order absorption process from the depot to the central compartment, parameterised in terms of the absorption constant (Ka, h^{-1}). A linear process (CLL, L/h) and a non-linear process, represented by the Michaelis-Menten parameters Vm (mg.h/L) and Km (mg/L), were used to describe the elimination from the central compartment. Both compartments were represented by a distribution volume (V2 +V3) linked by an inter-compartmental clearance Q. A lag time and the bioavailability factor F completed the set of fixed effect model parameters θs.

Results: The Pop PK model enabled estimation of alirocumab PK properties and individual exposures. The model also allowed for identification of covariates that explained inter-individual variability of alirocumab treatment: CLL was related to body weight and co-administration of statins, Km was related to free time-varying PCSK9 serum levels and V3 was related to age.

Conclusions: The PK of alirocumab is best described as non-linear, with target-mediated clearance, although the deviation from linearity is modest**.** Alirocumab PK parameters were estimated using the Pop PK model, with 4 main covariates identified that impact alirocumab PK. The model was used to predict alirocumab concentrations which were subsequently used to build a Pop PK/PD model (part 2).

III-20: *Paolo Mazzei* Population exposure-response modeling of oral nepadutant administration in infants with colic

P. Mazzei (1), E. Mezzalana (1), G. Smania (1), E.N. Jonsson (2), S. Jönsson (2), S Bouchene (2), M.O. Karlsson (2), S. Scartoni (1), A. Capriati (1)
(1) Menarini Ricerche S.p.A., Florence (Italy), (2) Pharmetheus AB, Uppsala (Sweden)

Objectives: Nepadutant is a potent antagonist of tachykinin NK2 receptors found to control the gastrointestinal hypermotility. In NIC-03, a phase IIa multicentre, randomised, double-blind, placebo controlled trial to study the efficacy of two oral nepadutant doses (0.1 or 0.5 mg/kg) in infants with colic, a population Exposure-Response (ER) analysis was performed. This analysis aimed to: i) develop an ER model based on observations of crying+fussing time and the previously developed population pharmacokinetic model ii) use the ER model to illustrate the performance of the studied dosing regimens in different body weight (WT) groups.

Methods: The population ER model was based on observations of length of crying+fussing time (min) within 2h intervals at baseline (72h prior dosing) as well as while on treatment (last 72h over 1 week placebo and nepadutant treatments). The model described i) the circadian rhythm in the response by the use of sum of cosine functions, ii) the increasing placebo effect versus time with an exponential time dependent model and iii) the increasing response with dose by a linear dose-response model. The effects of WT and AGE were assessed as continuous covariates on parameters of each sub-model. Final analysis dataset included 9945 observations of crying+fussing time/2h from 104 infants. Analyses were conducted using non-linear mixed-effects modelling as implemented in NONMEM [1].

Results: The inclusion of the linear dose-response relationship on top of the placebo model provided a statistically significant improvement in the description of data ($p<0.01$). The model predicted a change from baseline for the 0.5 mg/kg group of -36%, corresponding to a relative improvement of 29% over placebo. No statistically significant effect of AGE or WT was identified.

Conclusion: According to simulations, the population ER model well described the data and provided further support to the clinical efficacy data favouring nepadutant 0.5 mg/kg dose.

References:
[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.

III-21: *Litaty Céphanoée Mbatchi* Pharmacokinetics modelling of temsirolimus and its active metabolite

Litaty C. Mbatchi (1,2,3) Matthieu Gassiot (1,3), Philippe Pourquier (3), Michel Audran (4), Guilhem Roubaud (5), Alexandre Evrard (1,2,3),and Nadine Houede (3)
(1) Laboratoire de biochimie, Centre Hospitalier Universitaire (CHU) of Nîmes, Hôpital Carémeau, Nîmes, France ; (2) Laboratoire de Pharmacocinétique, Faculté de Pharmacie, Université de Montpellier, Montpellier, France (3) IRCM, Institut de Recherche en Cancérologie de Montpellier, Montpellier, F-34298, INSERM, U1194 France ; (4) Laboratoire de Biophysique, Faculté de Pharmacie, Université de Montpellier, Montpellier, France (5) Service d'oncologie médicale, Institut Bergonié Bordeaux

Objectives: To develop a PK model of temsirolimus and its active metabolite sirolimus, and to correlate the exposure with the antitumoral response and with pharmacogenetics markers.

Methods: In a multicentric phase II study, 16 bladder cancer patients received once weekly infusion of temsirolimus at the dose of 25mg. Whole blood sample were collected at 0 hours (predose) and at 0.5, 1, 2, 6, 24, 74, 96, and 168 hours after the start of the infusion during the first week. A HPLC-MS/MS method was validated in order to quantify temsirolimus and sirolimus its active metabolite. Plasma concentrations were fitted to a pharmacokinetic model using non-linear mixed-effects modelling implemented in NONMEM V7.2.0 [1]. Area Under Curve (AUC) of each molecule were calculated by using the individuals estimation of clearance (AUC=DOSE/clearance) and we also calculated the total AUC of the active coumpounds ($AUC_{TEMSIROLIMUS}$ + $AUC_{SIROLIMUS}$). Associations between pharmacokinetic parameters and efficacy or polymorphisms in genes that control the metabolisms of our compounds (*CYP3A4*, *CYP3A5, ABCB1* and *NR1I2)* were assessed.

Results: A 3-compartment model with zero-order infusion was shown to most adequately describe the concentrations of temsirolimus. For sirolimus, the active metabolite, a 2-compartment model with first-order input was found as the most adequate.

Conclusion: This model could help to optimize the dosing of temsirolimus for bladder patient and also in. for metastatic renal cancer, which is the main indication of temsirolimus.

References:
[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.
[2] https://www.pharmgkb.org/

III-22: *Johanna Melin* Semi-mechanistic modelling of the nonlinear hydrocortisone pharmacokinetics to enable extrapolation into paediatric patients

Johanna Melin (1)(2), Zinnia P Parra-Guillen (1), Niklas Hartung (1), Wilhelm Huisinga (3), Richard J Ross (4), Martin J Whitaker (5), Charlotte Kloft (1)
(1) Dept. of Clinical Pharmacy and Biochemistry, Insitute of Pharmacy, Freie Universitaet Berlin, Germany (2) and Graduate Research Training Program PharMetrX (3) Institute of Mathematics, Universitaet Potsdam, Germany (4) The University of Sheffield, UK (5) Diurnal Limited, Cardiff, UK

Objectives: Therapy optimisation of hydrocortisone (HC), synthetic cortisol, is challenging due to its nonlinear pharmacokinetics (PK) caused by several factors: i) cortisol is mainly bound with high affinity to corticosteroid binding globulin (CBG), and to a lesser extent to albumin and erythrocytes [1, 2, 3]. ii) The oral bioavailability of HC is dose-dependent, probably due to an increased first-pass metabolism or saturable absorption [2]. HC is equivalent to endogenous cortisol, and cannot be separated. The objective of this analysis was to characterise the PK of HC after administration of Infacort® (oral HC granules with taste masking) to healthy volunteers for future extrapolation.

Methods: Volunteers were suppressed with dexamethasone prior to receiving single doses of either 0.5, 2, 5 and 10 mg Infacort (n=16, study 1 [4]) or 20 mg Infacort and 20 mg HC iv (n=16, study 2) Total plasma concentrations were sampled up to 12 h post dose (rich sampling) and unbound concentrations (only study 2, sparse sampling) were analysed using ultrafiltration. A plasma protein binding model was established using unbound and total concentrations, and validated to previously published data [3]. The binding model was integrated into the disposition model, which was established in NONMEM 7.3 based on total concentrations. Predictive performance and parameter precision were assessed by visual predictive checks and bootstraping, respectively.

Results: A two compartment disposition model with a constant cortisol baseline (15 nmol/L, B1 method [5]), and considering both nonlinear and linear binding for HC described the data most accurately. Maximum binding capacity (B_{max}) was 500 nmol/L, and the equilibrium dissociation constant (K_d) was 12 nmol/L. The binding model successfully predicted the published data in [3]. The saturable absorption indicated a nonlinear process for the three highest doses. Estimating a dose-dependent bioavailability improved model performance, and resulted in a reduction in bioavailability of approximately 40% for the 20 mg dose.

Conclusions: A semi-mechanistic population pharmacokinetic model for HC in healthy volunteers has been established. The model will be used further to predict exposure in paediatric patients and evaluated in further clinical trial results.

Acknowledgment: The work is being carried out under a Cooperation Agreement between Freie Universitaet and Diurnal funded by the European Commission FP7 Grant (No. 281654 TAIN).

References:
[1] RD Toothaker, PG Welling. Effect of dose size on the pharmacokinetics of intreavenous hydrocortisone during endogenous hydrocortisone suppression. J Pharmacokinet Biopharm 10: 147-156 (1982)
[2] RD Toothaker, WA Craig. Effect of dose size on the pharmacokinetics of oral hydrocortisone suspension. J Pharm Sci 71: 1182-1185 (1982)
[3] EGWM Lentjes, FHTPM Romijn. Temperature-dependent cortisol distribution among the blood

compartments in man. J Clin Endocrinol Metab 84: 682-687 (1999)
[4] M Whitaker, S Spielmann. Development and testing in healthy adults of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency. J Clin Endocrinol Metab 100: 1681-1688 (2015)
[5] C Dansirikul, H Silber. Approaches to handle pharmacodynamics baseline responses. J PKPD 35:269-83 (2008)

III-23: *Evgeny Metelkin* Development of immune responce template forsystems pharmacology modeling of immunotherapy in oncology

Evgeny Metelkin, Antonina Nikitich, Oleg Demin Jr, Oleg Demin
Institute for Systems Biology (Moscow)

Objectives: Immunotherapy is a new class of cancer treatment that works by activation of immune response of patient to fight with tumor. The main aim of this study is to develop a tool facilitating the development new immunotherapies and their combinations.

Methods: A multidisciplinary team developed Immune Response Template (IRT) which represents family of ODE- based models including both models of individual immune cells and integrated simulation platform describing interactions of multiple immune cell types, cancer cells, soluble mediators, cell-cell contact effects (via surface molecules PD-1:PD-L1, CD40:CD40L) etc.

Results: The models was partially calibrated against publicly available *in vitro* and *in vivo* data including activation of T helper cells, CD40-ligand effect on dendritic and B cells (see Figure), production of cytokines by immune and cancer cells, half-lives immune cells etc.

Conclusions: IRT recapitulates essential immune response pathways, effect of immune response on tumor and vice versa. IRT will serve as a framework to facilitate understanding of mechanisms of action of different immunotherapies and their effects, predictive biomarkers identification, optimization of regimens and therapies combination, evaluation of new targets and stratification of subjects enrolled in clinical trials.

III-24: *Jonathan Mochel* Pharmacodynamics of the renin-angiotensin aldosterone system and blood pressure in relation to food intake in dogs

J.P. Mochel and M. Danhof
Department of Pharmacology, Leiden-Academic Centre for Drug Research, 2300 Leiden, The Netherlands

Objectives: Similar to humans, activation of the renin-angiotensin-aldosterone system (RAAS) is one of the key neurohumoral responses to the reduced cardiac output observed in canine congestive heart failure (CHF). Results from our previous research [1] showed that variables of the RAAS and blood pressure (BP) oscillate with significant day–night differences in dogs. The manipulation of feeding schedules has been shown to influence the rhythmicity of several physiological variables (e.g liver glycogen and heart rate) but the impact of timed feeding on the chronobiology of the renin cascade remains controversial. The objective of this work was to evaluate the effect of food intake on the pharmacodynamics of renin activity (RA) and BP in dogs.

Methods: In a first experiment, blood samples for measurement of RA were drawn from 18 dogs fed a normal-sodium diet at either 07:00, 13:00 or 19:00 h. In a second study BP was recorded continuously from six telemetered beagle dogs fed a similar diet at 07:00 or 19:00 h. Data were collected throughout 24-h time periods and analyzed by means of NLME models in NONMEM 7.2 using a combination of periodic functions. Model selection was based on statistical significance between competing models using the OFV obtained from NONMEM, graphical evaluation and validity of parameter estimates. Residual error estimates from the mathematical models were used as supportive information for evaluation of lack of fit.

Results: Cosine and surge models were able to reproduce the time-variant changes of the experimental data with good accuracy, as suggested by the quality of the standard goodness-of-fit diagnostics and the individual predictions. Our data show that the timing of food intake exerts a synchronizing effect on RA and BP, such that a 6 to 12-h delay in the dogs' feeding schedule triggers a shift of similar magnitude in the rhythm of these biomarkers.

Conclusions: Our results indicate that meal timing drives the periodicity of BP and RAAS-related variables in dogs. Activation of renin is a common neurohumoral feature of human and canine CHF [2]; information on the chronobiology of the RAAS in dogs therefore contributes to a better understanding of cardiovascular physiology in humans. Accumulating knowledge on the chronobiology of the RAAS and BP provides a strong scientific rationale for determining the optimum dosing time, thereby making the best usage of available cardioactive drugs.

References:
[1] Mochel JP, Fink M, Peyrou M, Desevaux C, Deurinck M, Giraudel JM, Danhof M. Chronobiology of the renin-angiotensin-aldosterone system in dogs: relation to blood pressure and renal physiology. Chronobiol Int. 2013;30(9):1144-59.
[2] Sisson DD. Neuroendocrine evaluation of cardiac disease. Vet Clin North Am Small Anim Pract. 2004;34(5):1105-26.

III-26: *Pablo Morentin Gutierrez* A population pharmacokinetic-pharmacodynamic model for AZD7687: Effects on plasma triacylglycerol after oral lipid tolerance test

Pablo Morentin Gutierrez, James Yates, Catarina Nilsson
AstraZeneca

Objectives: Measuring plasma triglyceride (TAG) by means of an Oral-Lipid-Tolerance-Test (OLTT) can determine the efficiency with which the individual uses lipid components that are linked with cardiovascular diseases. However, despite the wide use of OLTT in the development of potential new treatments, very limited PK/PD analysis of this type of data has been carried limiting the precision and power of the analysis of the data generated. A novel PK/PD model that describes the magnitude and duration of the effect of AZD7687[1] in the plasma TAG during an OLTT setting in humans, rats and mice is therefore proposed

Methods: AZD7687 is an inhibitor of acyl-CoA:diacylglycerol acyltransferase (DGAT1), which is involved in lipid absorption. PK and Plasma TAG time course data during OLTT following AZD7687 treatment was obtained both in animals and in humans[2,3]. In the PK/PD model, the introduction of exogenous TAG into the system is represented by a first order process from the lipid depot compartment (assumed to be the gut) to the central compartment (plasma). In addition, there is an endogenous production and removal of TAG from plasma described with a turnover model. It is postulated that AZD7687 inhibits the contribution of exogenous TAG into circulation. 1 or 2 compartment models with first order absorption was used to describe the PK of AZD7687 for the different species. Non-linear mixed effect modelling implemented in Phoenix NLME 1.3[4] was used to fit the model to the PK and TAG data

Results: PK was well described by the models used. The magnitude and duration of the effects of AZD7687 in the plasma TAG time course in an OLTT were very well captured by the model in all the species. Inter-individual variability was also adequately captured by the model. The resulting in vivo IC50s for AZD7687 in the new model were in very good agreement with previously published values (for rat[1] and human[2]) using more limited PK/PD analysis

Conclusions: This modelling approach provides a deeper understanding of the magnitude and time course of change on the plasma TAG excursion during an OLTT after treatment of AZD7687. It also provides a numerical quantification of the “in vivo” potency of the drug allowing robust comparison of the efficacy of AZD7687 across species as well as tools to simulate the expected results under different dosing schedules. Finally, the system parameters on the model can now will facilitate simulations for other compounds

References:
[1] J.G. Barlind, U.A. Bauer, A.M. Birch, S. Birtles, L.K. Buckett, R.J. Butlin, et al. Design and Optimization of Pyrazinecarboxamide-Based Inhibitors of Diacylglycerol Acyltransferase 1 (DGAT1) Leading to a Clinical Candidate Dimethylpyrazinecarboxamide Phenylcyclohexylacetic Acid (AZD7687). J. Med. Chem. 2012, 55:10610−10629
[2] H. Denison, C. Nilsson, M. Kujacic, L. Lofgren, C. Karlsson, M. Knutsson. Proof of mechanism for the DGAT1 inhibitor AZD7687: Results from a first-time-in-human single-dose study. Diabetes, Obesity and Metabolism. 2013, 15:136-143
[3] H. Denison, C. Nilsson, L. Lofgren, A. Himmelmann, G. Martensson, M. Knutsson. Diacylglycerol acyltransferase 1 inhibition with AZD7687 alters lipid handling and hormone secretion in the gut with

intolerable side effects: a randomized clinical trial. Diabetes, Obesity and Metabolism. 2014, 16: 334–343.
[4] Pharsight, Certara USA, Inc, 100 Overlook Center, Suite 101, Princeton, NJ 08540 USA

III-27: *Michael Morimoto* A quantitative physiologic model of the interaction of nutrition and infection in determining the energy available for growth

Michael Morimoto (1,2), Lyn Powell (1,2), Rajalakshmi Santhakumar (1,3), Aaron Gowins (1,4), Joanne Arsenault (1,5), Carson Chow (1,4), Rukmini Kumar (1,3)
(1) HBGDki community, (2) Lynx Bioconsulting, USA, (3) Vantage Research, India, (4) NIH, USA (5) University of California at Davis, USA

Objectives: To develop a quantitative physiologic model that represents the major causal dependencies relating nutritional status and enteric pathogen exposure to macronutrient and energy availability in order to better understand and predict effective interventions for growth faltering children in low- to middle-income countries.

Methods: A thorough review of public literature guided the structural development of a 20-state nonlinear differential equation model representing the major mechanisms believed to causally connect nutrition and pathogen exposure to macronutrient and energy available for metabolism and growth. Published quantitative data and qualitative expectations were used for calibration, validation, refinement of the functional forms of the differential equations, and enforcement of local behavior around phenotypes (e.g., parameter values guaranteeing stability of healthy equilibria).

Results: Despite the wide range of biological domains and data sources combined into the model, it is able to exhibit larger-scale behaviors that result from mechanistic interactions of the smaller subsystems. Most notably, the model is able to confirm the prevailing hypothesis on the etiology of environmental enteropathy [1, 2], i.e., a) malnourishment leads to an increased susceptibility to infection, b) recovery time of intestinal damage after acute pathogen infection is increased because of malnutrition, and c) the increased duration of intestinal damage leads to a prolonged duration of malabsorption, causing a further deterioration of nutritional status. The model predicts that, with repeated exposure to enteric pathogens, even children with age-appropriate required gross intake may incur a cumulative energy deficit large enough to fall off a “normal” growth trajectory. Simulated reproduction of these behaviors confirms the “synergy”/super-additivity that is often reported between the effects of undernourishment and infection on growth faltering [1].

Conclusions: Model simulations suggest that reductions in macronutrient and energy availability for metabolism and growth are not just the result of deficient dietary intake, but may also arise due to repeated exposure to pathogens. Effective interventions should therefore be focused on increasing both nutritional quantity/quality and sanitation/water quality/hygiene.

Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative

References:
[1] Guerrant, R. L., Oriá, R. B., Moore, S. R., Oriá, M. O., & Lima, A. A. (2008). Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutrition reviews*, *66*(9), 487-505.
[2] Lunn, P. G. (2000). The impact of infection and nutrition on gut function and growth in childhood. *Proceedings of the Nutrition Society*, *59*(01), 147-154.

III-28: *Samer Mouksassi* Primary microcephaly: do all roads lead to Rome?

Samer Mouksassi(1) and Shasha Jumbe(2)
(1) Certara Strategic Consulting, (2) Bill and Melinda Gates Foundation

Objectives: Symmetric intrauterine growth restriction (IUGR) has been used to describe a growth pattern when all biometric measurements appear affected to the same degree, whereas asymmetric IUGR has been used to characterize a small abdominal circumference (AC) compared to other growth parameters. Asymmetric IUGR would then show abnormal ratios such as head circumference (HC)/AC or femur length (FL)/AC ratio. The objectives of this analysis were: i) to determine the joint probability distributions of growth parameters describing Weight/Length and Head circumference (WT/LEN/HC) from 0 to 24 months of age and ii) to study symmetry across the three growth measures parameters in order to provide useful quantitative guidance to Zika clinicians and researchers on measurements of an individuals with a normal/mild-to-moderate/small head relative to other anthropometric measures.

Methods: A joint parametric nonlinear mixed effects model was built using the QRPEM fitting engine. Several parametric models were tested such as an exponential growth with and without decelerating growth rate. Limited covariate testing was done including covariate such as country site, sex, and socioeconomic factors. The model goodness of fit was assessed using graphical tools and simulation based diagnostics (VPC). Parameter uncertainty was obtained from bootstrap resampling.

Results: A joint nonlinear deceleration model for WT/LEN/HC best fitted the data (115060 observations from 1568 subjects) with a full random effects variance covariance matrix. The between subject variability ranged from 50 % (Weight rate of growth) to 10 % (Length at zero month). Overall, there was a good agreement between the observed and simulated data 1 to 97 percentiles. Country and sex were kept in the model. Parameters uncertainty was < 30%. The model could accurately simulate correlated longitudinal data of WT/LEN/HC from 0-24 months and predict probability of stunting as well as the trajectories of HC growth including microcephaly conditional on WT and LEN. WT/HC, LEN/HC and WT/LEN standards were generated.

Conclusions: These results address a key aspect of characterizing WT/LEN/HC relationships and predicting their evolution over time for a specific child not just the population. Potential application of this model includes individualized trivariate growth trajectories for early detection of serious conditions such as stunting and microcephaly.

References:
[1] Peleg et al. Intrauterine Growth Restriction: Identification and Management. *Am Fam Physician.* 1998 Aug 1;58(2):453-460

This work is presented on behalf of the Healthy Birth, Growth and Development knowledge integration (HBGDki) community and sponsored by the Bill & Melinda Gates Foundation.

III-29: *Morris Muliaditan* Prediction of the exposure of anti-tuberculosis drugs in lung tissue: implications for dose selection

Morris Muliaditan (1,2), Donato Teutonico (3), Fatima Ortega (4), Santiago Ferrer (4), Oscar Della Pasqua (1,2)

(1) UCL School of Life and Medical Sciences, London, UK, (2) GlaxoSmithKline, London, UK, (3) Bayer Technology Services, Leverkusen, Germany, (4) GlaxoSmithKline Diseases of Developing World (DDW) Medicines Development Campus, Tres Cantos, Madrid, Spain.

Objectives: The rationale underpinning dosing regimens of modern short-course therapy for tuberculosis (TB) remains empirical. Characterising the time course of drug concentrations in the lung can provide better understanding of the exposure-response relationship at the site of action and inform a more robust dose rationale. A physiologically-based pharmacokinetic (PBPK) model in mice was developed using isoniazid (INH) and rifampicin (RMP) as paradigm compound. Human lung tissue and plasma concentration were predicted from the mice PBPK model with the objective of highlighting the difference between drug exposure in plasma and in tissue.

Methods: Mouse plasma INH concentrations were collected following a single 10 mg/kg intravenous (IV) or 0.1-25 mg/kg oral (PO) administration. Plasma RMP concentrations were collected following single 12 mg/kg IV or 1-100 mg/kg PO, supplemented with literature data from mice who received single dose 0.33-810 mg/kg PO (1). Lung tissue concentrations were measured after administration of 0.5, 5 and 25 mg/kg (INH) or 10 and 100 mg/kg (RMP). Predicted human plasma AUC0-24 were compared against simulated values using published PK models (2,3). Plasma and lung concentration versus time profiles based on WHO recommendations were simulated in virtual patients. The adequacy of each regimen was assessed taking into account the variability in AUC0-24. Population PK simulations were performed in NONMEM 7.3 and the PBPK model was developed in PK-Sim and MoBi (4). All animal studies were ethically reviewed and carried out in accordance with European Directive 86/609/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

Results: The PBPK model adequately described INH and RMP lung tissue concentration in mice and closely predicted human plasma concentrations. The median INH AUC0-8 plasma to lung ratio was 1.03, 1.05 and 0.91 after administration of respectively 0.55, 5.11 and 25.70 mg/kg, whereas the RMP median AUC0-8 plasma-lung ratio was 0.48 and 1.25 following 10 and 100 mg/kg. Evaluation of the weight bands revealed that WHO recommended regimens yielded the lowest exposure in patients weighing less than 40 kg.

Conclusion: In summary, current analysis suggests that INH levels in tissue do not differ considerably from levels in plasma whereas RMP exposure in the lung is dose dependent. Patients with less than 40 kg are potentially underexposed to both drugs as compared to those with higher body weight.

References:

[1] Jayaram R et al. (2003). Pharmacokinetics-Pharmacodynamics of Rifampin in an Aerosol Infection Model of Tuberculosis. Antimicrob Agents Chemother 47: 2118-24
[2] Wilkins J et al. (2011). Variability in the population pharmacokinetics of isoniazid in South African tuberculosis patients. Br. J Clin Pharmacol 71:51-62
[3] Smythe et al. (2012). A Semimechanistic Pharmacokinetic-Enzyme Turnover Model for Rifampin Autoinduction in Adult Tuberculosis Patients. Antimicrob. Agents Chemother 56: 2091-2098
[4] Eissing T et al. (2011). A computational systems biology software platform for multiscale modeling and

simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front. Physio 24: 2-4

III-30: *Zufar Muliukov* Modeling the effect of ranibizumab on central retinal thickness in patients with wet age-related macular degeneration

Zufar Mulyukov, Amy Racine, Etienne Pigeolet
Novartis, Basel, Switzerland

Objectives: The progression of the wet form of age-related macular degeneration (wet AMD) and the effect of the anti-VEGF ranibizumab on disease progression in terms of best corrected visual acuity (BCVA) has been well characterized by drug-disease models [1-2]. The aim of this analysis is to develop a model describing the effect of ranibizumab on central retinal thickness (CRT) in anti-VEGF treatment naïve patients with wet AMD. CRT is one of few anatomical features used by ophthalmologists along with BCVA to decide on treatment (dis)continuation. The anti-VEGF effect on CRT is much faster than its effect on BCVA; to describe the quick onset accurately, retinal thickness assessments within first few days of treatment are needed.

Methods: We developed a nonlinear mixed effect (NLME) indirect response kinetic-pharmacodynamic (K-PD) [3] model to describe CRT change with time during treatment with ranibizumab. The effect of vitreous ranibizumab injection was modeled as inhibition of CRT production rate k_{in} using E_{max} function of the drug concentration. The vitreous PK was described as linear elimination with half-life $T_{1/2}$ = 9 days without inter-subject variability. The data from four clinical studies (PIER, MARINA, EXCITE and SUSTAIN) including approximately 800 patients in total are used to fit the model. The treatment arms included monthly, quarterly and pro re nata (PRN) intravitreal injections of 0.3 mg and 0.5 mg doses, as well as sham injections.

Results: The mean retinal thickness in sham treated arms did not change throughout the studies period. The effect of ranibizumab treatment on CRT was large, with a decrease of about 100 um from a baseline of approximately 320 um, and relatively fast with a decrease in thickness of about 60 um occurring within the first week after the first injection. Quarterly treatment arms demonstrated fluctuations in mean CRT between injections, leading to average loss of about half of the effect within three months after an injection.

Conclusions: The developed K-PD turnover model captured major features of CRT behavior under ranibizumab treatment in patients with wet AMD, and, together with BCVA models, may enable more accurate simulations of adaptive treatment regimens such as PRN dosing.

References:

[1] Lu, Tong, et al. "Population Analysis of wet-AMD Disease Progression and The Therapeutic Effect of Ranibizumab." PAGE 2012. Abstracts of the Annual Meeting of the Population Approach Group in Europe.
[2] Weber at al. "Bayesian Drug Disease Model with Stan - Using published longitudinal data summaries in population models." PAGE 2014. Abstracts of the Annual Meeting of the Population Approach Group in Europe.
[3] Jacqmin, Ph, et al. "Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K–PD model." Journal of pharmacokinetics and pharmacodynamics 34.1 (2007): 57-85.

III-31: *Silke München* Population Pharmacokinetics of Voriconazole in pediatric cancer patients - assessing new dosing strategies

Silke E. München (1), Stephanie Pieper (2), Uwe Kirchhefer (3), Carsten Müller (4), Judith Moskovits (5), Thomas Lehrnbecher (5), Andreas H. Groll (2), Georg Hempel (1)
(1) Department of Pharmaceutical and Medicinal Chemistry, Clinical Pharmacy, Westfälische Wilhelms-Universität Münster, Germany, (2) Department of Pediatric Hematology/Oncology, University Children's Hospital, Münster, Germany, (3) Institute of Pharmacology and Toxicology, Westfälische Wilhelms-Universität Münster, Germany, (4) Division of Therapeutic Drug Monitoring, Department of Pharmacology University Hospital of Cologne, Germany, (5) Division of Pediatric Hematology and Oncology, Hospital for Children and Adolescents, Johann Wolfgang Goethe-University, Frankfurt, Germany

Objectives: In order to predict new dosing regimens to receive more sustainable trough concentrations in the supposed range of 1 – 6 mg/L, a population pharmacokinetic model for voriconazole including children younger than two years old was developed.

Methods: Plasma concentrations were obtained from an open-label study on PK in 24 paediatric patients (0.5 to 21 years) receiving both i.v. and oral voriconazole as prophylactic treatment. Non-linear mixed effects modelling (NONMEM 7.2) was used to develop the pharmacokinetic model based on the model developed by Friberg et al. [1].
Model diagnostic plots were performed using R in combination with the Xpose package. The final model was evaluated internal and externally. Subsequently Monte – Carlo Simulations were performed to test different dosing regimens.

Results: A two compartment model with first order absorption and non-linear Michaelis-Menten elimination was found to most adequately describe the pharmacokinetics of voriconazole (VMAX=61.6 mg/h/70kg, V1=237 L/70kg, Q=23.5 L/h/70kg, V2=685 L/70kg, F= 61.7 %, Km = fixed to 1.15 mg/L, Ka = fixed to 1.19 h^{-1}). Inter-individual variability on VMAX (67.7%), V1 (74.2%), Q (51.2%) and F (60% as logistic transformation) and residual variability (proportional error 15.6%, additive error 0.013 mg/L) were assessed. Allometric scaling with a fixed exponent of 0.75 on body weight for VMAX and Q, and body weight on V1 and V2 was used.
A three times per day (TID) regimen with a loading dose of 9mg/kg TID followed by 6mg/kg TID maintenance dosing from day 2 onward was simulated resulting in an increase in the percentage of patients attaining the target trough concentration above 1mg/L after 24h from 9% to 43% relative to the currently recommended dosing of 9mg/kg BID on day 1 followed by 8mg/kg BID maintenance dosing. Measured trough concentrations after 120h resulted in 42.4% patients reaching the target trough concentration for the currently recommended BID dosing. The TID regimen with an initial loading dose for 24h, 48h and 72h resulted in 54.5%, 57.2% and 61% adequately treated patients, respectively.

Conclusions: Voriconazole pharmacokinetics is highly variable and therapeutic drug monitoring is recommended. With our simulated TID regimen, more patients reached adequate trough concentrations in the first 24h of treatment. In the further course of treatment, the difference in adequately dosed patients was lower.

References:
[1] Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated Population Pharmacokinetic Analysis of Voriconazole in Children, Adolescents, and Adults. *Antimicrob. Agents Chemother*. (2012) 56(6):3032-3042

III-32: *Cynthia Musante* The International Society of Pharmacometrics' Special Interest Group on Quantitative Systems Pharmacology: Developing a community and advancing a field

CJ Musante (1), S Ramanujan (2), M Zager (3), V Damian (4), M Weis (5), J Woodhead (6)
(1) Pfizer Inc, Cambridge MA USA, (2) Genentech Inc, South San Francisco CA USA (3), Janssen Pharmaceutical Companies of Johnson & Johnson, San Diego CA USA, (4) GlaxoSmithKline, King of Prussia PA USA (5) Rosa & Co, San Carlos CA USA, (6) DILIsym Services, Inc, Research Triangle Park NC USA

Objectives: Quantitative Systems Pharmacology (QSP) has been described as the "quantitative analysis of the dynamic interactions between drug(s) and a biological system that aims to understand the behavior of the system as a whole…" [1]. The field, which has emerged at the interface of engineering, pharmaceutical sciences and systems biology, is realizing increased adoption in pharmaceutical research and development with the hope of improving the efficiency of getting new medicines to patients in need. With the emergence of this field, there is greater need for sharing and dissemination of learnings and coordination of efforts. To this end, the International Society of Pharmacometrics (ISoP) initiated a Special Interest Group on QSP (QSP SIG) with aims to: advance the science of QSP by fostering a community for the exchange of ideas and knowledge; promote the application of QSP in drug development and regulatory decision-making; develop and maintain information resources for its members, including establishment of "best practices", and; facilitate communication and advance knowledge through sponsored sessions at professional meetings, white papers, discussion groups, and publications.

Methods: The SIG has initiated numerous efforts to support its mission. Multiple programming sessions were contributed and held at professional conferences. Member-driven working groups have been formed that focus on specific topics of interest, including: GPS for QSP; QSP Workflows and Methodologies; Software and Tools; The Interface of QSP and Pharmacometrics; and Advancing the Role of QSP in Regulatory Interactions. The SIG is actively working with QSP-related communities in ASCPT, AAPS, and FIP to ensure consistent and cooperative efforts.

Results: In its first year, the SIG has grown to over 100 members, with a leadership team and steering committee that includes industry, regulatory, nonprofit, and academic representatives from the United States, Europe, and Asia. Tutorials and white papers from these working groups are already being developed and shared on our website.

Conclusions: The ISoP QSP SIG is actively promoting the sharing and dissemination of QSP-related content to advance this field and its continued application in pharmaceutical research & development. We welcome participation, collaboration, and contributions from all interested parties and organizations.

References:

[1] van der Graaf PH, Benson N. Systems pharmacology: bridging systems biology and pharmacokinetics-pharmacodynamics (PKPD) in drug discovery and development. Pharm Res. 2011 Jul;28(7):1460-4. doi: 10.1007/s11095-011-0467-9. Epub 2011 May 11.

III-33: *Karin Nelander* Longitudinal dose-response modelling as primary analysis of a clinical study

Bengt Hamrén, Susanne Johansson, Karin Nelander and Magnus Åstrand
AstraZeneca R&D, Gothenburg, Sweden

Objectives: ANOVA or analysis of covariance (ANCOVA) is commonly used as the primary analysis for clinical studies. For study designs with repeated measurements Mixed-Effect Model Repeated Measure (MMRM) is often used as either primary or secondary analysis. However, for studies including >1 dose strength, one drawback for both methods is that no information is obtained for doses not tested in the study. The objective of this work is to evaluate, both in terms of power and type 1 error, longitudinal dose-response modelling of all measured data with the aim of estimating treatment effect at end of study.

Methods: Clinical trial simulations of a placebo controlled multi dose HbA1c study with end of study HbA1c treatment effect as the primary endpoint were performed to compare ANCOVA, MMRM and longitudinal dose-response modelling (here LDRM) with respect to power and type 1 error. Repeated measurements of HbA1c were simulated using an indirect response model with a dose dependent inhibitory treatment effect on k_{in}. Model parameters for simulations were set based on observed data from in-house studies. Analyses were performed both after all patients have completed the study, and also at an interim when about half of the patients had entered the study, not all of them having complete data. For the evaluation of power, 1000 studies were simulated with two efficacious doses of a hypothetical drug. Type one error was estimated from the simulation of 10000 studies, where none of the two doses had any effect.

For HbA1c the within individual variability is relatively low compared to the total variability. To broaden the scope, simulations with higher within individual variability were also performed.

Simulations were performed in R (version 3.2.2, the R Foundation for Statistical Computing) and analyses were performed in SAS (version 9.3, SAS Institute Inc., Cary, NC, USA).

Results: The simulations show that the LDRM performs in line with the ANCOVA and the MMRM, both with respect to power and with respect to type 1 error. The LDRM provided somewhat better power compared to ANCOVA, and also to MMRM, when the full study was analysed but more so at the interim. This difference was even more pronounced in the case of a higher within individual variability.

Conclusions: The longitudinal dose-response modelling can provide more informed decision making without losing power or inflating type 1 error.

III-34: *Xavier Nicolas* Modelling and simulation of alirocumab - Part 2: Population pharmacokinetic/pharmacodynamic analysis using an indirect response model to link drug concentrations with LDL-C

Xavier Nicolas (1), Nassim Djebli (1), Clemence Rauch (1), Aurélie Brunet (1), Fabrice Hurbin (1), Jean-Marie Martinez (1), David Fabre (1)
(1) Sanofi, Montpellier, France

Objectives: Alirocumab, a monoclonal antibody against PCSK9, significantly lowers LDL-C. The objective of this analysis was to develop and qualify a Pop PK/PD model for alirocumab based on pooled PK and PD data obtained from 13 Phase I/II/III clinical trials. We explored the potential relationships between the Pop PD parameters and demographic covariates, relevant co-administration, type of disease and relevant biologic constants.

Methods: From a dataset comprised of ~2800 patients (~14346 LDL-C concentration-time points), a two-staged approach was used and this Pop PK/PD model followed-on from the Pop PK model (part 1). Individual PK parameters from the Pop PK model were used to estimate alirocumab concentrations. An indirect response model with Hill coefficient, parameterised with increasing LDL-C elimination was developed to relate alirocumab concentrations with LDL-C values.

Results: The Pop PK/PD model allowed the characterisation of the PK/PD properties of alirocumab in the target population and estimation for each patient of LDL-C concentrations and derived PD parameters (ΔLDL-C_{max} and ΔLDL-C_{trough}). The relationship between several significant parameter-covariates was retained in the model, including 6 covariates on Emax, specifically time-varying total PCSK9, sex, age, weight, baseline free PCSK9 and statin co-administration. Nevertheless, this high number of covariates included in the model did not greatly impact model-derived PD parameters.

Conclusions: None of the covariates included in the model had a clinically significant impact on LDL-C reduction.

III-35: *Jaeseong Oh* Simultaneous population pharmacokinetic analysis of VVZ-149 and its active metabolite in healthy volunteers

Jaeseong Oh (1), Doo H. Lee (2), Sunyoung Cho (2), Su-jin Rhee (1), Kyungho Jang (3), Seonghae Yoon (1), Kyung-Sang Yu (1), In-Jin Jang (1), Jae-Yong Chung (4)

(1) Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea; (2) Vivizon, Inc. Seoul, Korea; (3) Department of Clinical Pharmacology and Therapeutics, CHA Bundang Medical Center, CHA University, Seongnam, Gyeonggido, Republic of Korea; (4) Department of Clinical Pharmacology and Therapeutics, Seoul National University Bundang Hospital, Seongnam, Gyeonggido, Republic of Korea

Objectives: VVZ-149, a dual antagonist on GlyT2 and 5HT2A, is an investigational analgesic product targeted for post-operative pain. The clinical therapeutic concentration range of VVZ-149 including its active metabolite (VVZ-368) was expected to be 600 – 1900 μg/L, according to the preclinical study results. The aim of this study was to develop a population PK model for VVZ-149 and VVZ-368.

Methods: A randomized, double-blind, single ascending-dose (SAD) and multiple ascending-dose (MAD), placebo-controlled clinical trial was conducted in 67 healthy volunteers (NCT01905410). Subjects intravenously received 0.25-8 mg/kg of VVZ-149 in SAD study and 8-14 mg/kg/day for three days in MAD study. Serial blood samples were collected to analyze plasma concentration of VVZ-149 and VVZ-368. A total of 2,042 plasma concentrations were pooled to develop a population PK model using the nonlinear mixed-effects method in NONMEM (ver. 7.3). The First-Order Conditional Estimation with Interaction estimation method was implemented, which was followed by model qualification using bootstrapping and visual predictive checks (VPCs).

Results: The final model consisted of 3 compartments: central (1) and peripheral (2) for VVZ-149 and central for VVZ-368 (3). All transfers were described with first-order processes. Inter-subject variabilities were modelled by exponential error models and proportional error models were used to account for intra-subject variabilities of both VVZ-149 and VVZ-368. The typical values of population pharmacokinetic parameters were; clearance of VVZ-149 (CL, $48.8 \cdot (\text{creatinine clearance}/111)^{0.51}$ L/h), central volume of distribution (V1, 19.0 L), inter-compartmental clearance (Q, 88.5 L/h), peripheral volume of distribution (V2, 78.5 L), metabolic clearance of VVZ-149 converted into VVZ-368 (CL_{pm}, 1.01 L/h), clearance of VVZ-368 (CL_m, 2.73 L/h). The inter-individual variability (CV%) of CL, V1, V2 and CL_{pm} were 18.6%, 34.7%, 22.1% and 46.8%, respectively. Model evaluation by goodness of fit plots, bootstrapping and VPCs suggested that the proposed model was adequate and robust with good precision. For the therapeutic purpose, a loading-maintenance dose of VVZ-149 (loading dose: 2.6 mg/kg/h for 0.5 hour; maintenance dose: 0.9 mg/kg/h) were predicted to be proper dosage regimen to achieve the effective concentration range.

Conclusions: The final model adequately described the observed plasma concentrations of VVZ-149 and VVZ-368 in healthy male volunteers. The simulated dose regimen can be applied in further drug development.

III-36: *Boram Ohk* Population Pharmacokinetic modeling of Tacrolimus in Healthy Korean Subjects

Boram Ohk, Joomi Lee, Mi-Ri Gwon, Bo Kyung Kim, Hae Won Lee,Hyun-Ju Kim, Sook Jin Seong, Woo Youl Kang and Young-Ran Yoon
Dep. of Biomedical Science, BK21 Plus KNU Bio-Medical Convergence Program for Creative Talent and Clinical Trial Center,

Objectives: Tacrolimus, an immunosuppressive agent that has been commonly used to prevent rejection after organ transplantation, is known to have substantial inter-individual pharmacokinetic (PK) variability and narrow therapeutic range. Tacrolimus is primarily metabolized by the cytochrome P450 enzymes CYP3A4 and CYP3A5. Differences in activity of metabolizing enzymes are responsible for a large part of the variability in pharmacokinetics. The aim of this study was to develop a population PK model of tacrolimus in healthy Korean subjects.

Methods: This study was conducted in 29 healthy Korean subjects. All received 0.075mg/kg oral dose of tacrolimus. Blood samples were drawn at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after dosing. Plasma tacrolimus concentrations were analyzed using liquid chromatography mass spectrometry (LC/MS). A population PK analysis was conducted using NONMEM (Ver. 7.2).

Results: A 2-compartment model with first-order absorption provided the best fit from healthy subjects. Estimates of the population PK parameter were as follows; CL, 12.5 L/h; Vc, 19.6 L; Ka, 0.545 h-1; ALAG, 0.363 h; Vp, 359 L; Q, 26.4 L/h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model.

Conclusions: The population PK model was successfully developed and reasonable parameters were obtained. Further study will be required to find out covariates affecting the PK parameters.

[This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science, ICT & Future Planning, Republic of Korea (NRF-2013M3A9B6046416), by the Industrial Core Technology Development Program (10051129, Development of the system for ADME assessment using radiolabeled compounds) funded by the Ministry of Trade, Industry & Energy, by a grant of the Korean Health Technology R&D Project through the Korea Health Industry Development Institute(KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI14C2750,HI15C0001).]

III-37: *Andrés Olivares-Morales* Combining population with physiologically-based pharmacokinetic (PBPK) models for oral drug absorption: Predicting the segmental bioavailability differences of R-oxybutynin and its main metabolite using a middle out approach.

Andrés Olivares-Morales (1), Avijit Ghosh (2), Amin Rostami-Hodjegan (1,3) and Leon Aarons (1)
(1) Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, University of Manchester, Manchester, UK.(2) Janssen Pharmaceutica, Spring House, PA, USA. (3) Certara, Blades Enterprise Centre, Sheffield, UK.

Objectives: The minimal Segmented Absorption and Transit (mSAT) model has been recently proposed and applied to mechanistically predict the bioavailability differences observed for oxybutynin's (OXY) OROS formulation compared to its immediate release (IR) tablet [1]. The aim of the present study was to expand and refine this model for the pharmacokinetic (PK) prediction of both R-OXY and its main metabolite, N-desethyloxybutynin (DEOB), IR and OROS, and to describe the high interindividual variability (IIV) observed in their PK response using the so-called "middle out" approach to develop a population PBPK (pop-PBPK) model for OXY and DEOB

Methods: The mSAT model was expanded to account for the formation of R-DEOB in the gastrointestinal tract and the liver, whereas its disposition was described by a semi-physiological model. The model was implemented in NONMEM 7.3 as a system of 26 ODEs using the ADVAN13 subroutine and then fitted to R-OXY/DEOB plasma concentrations obtained after the administration of three IR tablets (over 24 hours) to 41 healthy volunteers with rich sampling. The parameter estimation was aided with the use of NONMEM's prior functionality to obtain maximum *a posteriori* (MAP) estimates [2]. The goodness of fit was evaluated by visual predictive checks (VPCs) and the model performance was evaluated by simulating the PK profiles of R-OXY/DEOB after the administrations of one 10 mg OROS tablet as well as by simulating a drug-drug interaction (DDI) study between OXY OROS and ketoconazole (KTZ) 200mg BID

Results: The model provided a good fit to the observed data of R-OXY/DEOB for the IR tablets, as seen in the VPCs. Using the parameter estimates obtained from the IR fit and the *in vitro* release profile as input parameters, the mSAT model was able to capture both the PK and IIV observed for R-OXY/DEOB after the administration of a 10mg OROS formulation. The simulated DDI study between OXY OROS and KTZ BID predicted a 2.5 to 3.2 fold increase (mean 2.8) in the exposure of the parent drug, whereas for the metabolite the exposure remained almost unaffected. This was consistent with information provided in the product label [3].

Conclusions: The pop-PBPK model allowed the refinement of the previously developed mSAT model for OXY and the description of the high IIV observed in PK profiles. This approach allowed a better understanding of the PK of OXY and its metabolite.

References:

[1] Olivares-Morales A. Aarons L., Rostami-Hodjegan A. Predicting the Higher Bioavailability Observed for Oxybutynin's OROS Formulation Compared to the Immediate-Release (IR) Tablet Using a Novel Simplified Absorption PBPK Model. Presented at 2015 AAPS Annual Meeting and Exposition; Poster T33171 [http://abstracts.aaps.org/Verify/AAPS2015/PosterSubmissions/T3317.pdf]
[2] Gisleskog, P., et al. (2002) Use of Prior Information to Stabilize a Population Data Analysis. Journal of

Pharmacokinetics and Pharmacodynamics 29(5-6): 473-505.
[3] U.S. Food and Drug Administration (2015). Ditropan XL® Product Label. Retrieved 06/01/2015, 2015, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/17577se8-033,18211se8-016,20897slr010_ditropan_lbl.pdf

III-38: *Per Olsson Gisleskog* Predicting the effects of combining broadly neutralizing antibodies (bNabs) binding to different HIV viral epitopes

Per Olsson Gisleskog (1), Mike Seaman (2), Pervin Anklesaria (3), Shasha Jumbe (3)
(1) SGS Exprimo NV, (2) Beth Israel Deaconess Medical Center-Harvard Medical School, (3) Bill and Melinda Gates Foundation

Objectives: Promising findings demonstrate that broadly neutralizing antibodies (bNabs) significantly reduce viral loads in people living with HIV—giving hope for its eventual use in treatment and cure strategies. The objective here was to model the inhibition caused by a range of bNAbs across a panel of 199 clade-C HIV-1 virus strains, using nonlinear mixed effects modelling, and to predict the effects of combining bNAbs binding to different viral epitopes in order to support programmatic decision-making.

Methods: A panel of bNabs targeting different epitopes were tested in a highly quantitative pseudovirus neutralization assay using TZM-bl target cells [1] on a panel of 199 viral clones. Neutralization curves of 9 different bNabs, binding to envelope protein, top of the trimer, or to same site as the human HIV receptor CD4, in the 0.000128 to 10 ug/mL concentration range, were available for analysis. Sigmoidal Emax models were fitted to the data from each bNAb, including between-strain variability on E0, IC50, and the Hill factor. For combinations of bNAbs, the effects were predicted using the principles of Loewe interaction and Bliss independence [2] and were compared to the observed inhibition in assays using these combinations. From the model, a good estimation of inhibition effects- the concentration giving at least 80% inhibition in 80% of viruses types, the IC80(80), could be estimated. The FOCE method and NONMEM 7.2 was used to fit the data.

Results: For each bNAb, the inhibition curves varied widely between the virus strains. Notably, some bNabs do not always achieve 100% neutralization even at high concentrations. Despite this challenge, data were well fitted using a sigmoidal Emax model which included a mixture model for IC50. Even so, the variability in IC50 within each mixture subset remained large.
IC50s generally correlated across strains for bNAbs binding to the same epitope. Predictions using the Bliss independence method agreed well with the observed effect of combinations.

Conclusion: In vitro data of bNAb effects in neutralizing HIV-1 virus showed a highly variable potency between viral strains. Data could be well fitted using sigmoidal Emax models with a mixture model on IC50. When assuming Bliss independence, the model proved predictive for the effects of combinations of bNAbs binding to different viral epitopes. The bNab combinatorics predictive platform is firmly at the core of data-driven decision-making for the bNab program.

References:

[1] Kong, R., Louder, M. K., Wagh, K., Bailer, R. T., deCamp, A., Greene, K., … Mascola, J. R. (2015). Improving Neutralization Potency and Breadth by Combining Broadly Reactive HIV-1 Antibodies Targeting Major Neutralization Epitopes. *Journal of Virology*, *89*(5), 2659–2671.
[2] Berenbaum, M. C. (1989). What is synergy? *Pharmacol Rev*, *41*, 93–141

III-39: *Mohamed Omari* Modelling of glucose-insulin metabolism and its effect on the estrous cycle in bovine

Mohamed Omari, Julia Plöntzke, Mascha Berg, Susanna Röblitz
Zuse Institut Berlin (ZIB), Takustr. 7, 14195 Berlin

Objectives: To develop a mechanistic mathematical model of glucose-insulin and to investigate its effect on the dynamic of the hormonal cycle in dairy cows.

Methods: A mechanistic mathematical model of glucose-insulin is developed based on the biological knowledges and experimental data [1,2,3]. The mathematical model describes the dynamical behaviour of insulin and glucose in the blood and in the tissues under different diet fractions. This model is linked to the bovine hormonal cycle that has been developed earlier in our group [4,5]. The model simulates periodic estrous cycles lasting 21 days, describing the dynamic of follicles, the corpus luteum and the key reproductive hormones regulating the system.

Results: Simulation results show that the glucose-insulin model is able to simulate reasonably the dynamics of the glucose and insulin within their physiological ranges under different diet regimen of the dry matter intake. In addition, by linking this model to the bovine estrous cycle, a selected diet restrictions show to cause an effect on the key reproductive hormones regulating the cycle, in particular an effect on the follicular development.

Conclusions: Formulating a mathematical model that simulates the effect of metabolic factors on bovine fertility will improve our understanding on the underlying biological processes without the need for new animal experiments and thereby assist in developing strategies again declined fertility in dairy cows.

References:
[1] CK Reynolds, Florida ruminant nutrition symposium, 143-154 (2005).
[2] JM Berg, JL Tymoczko, L Stryer, Biochemistry, WH Freeman, 5th edition Chapter 21, Glycogen Metabolism, (2002).
[3] R Pfuhl, O Bellmann, C Kuhn, F Teuscher, K Ender, J Wegner, Archiv für Tierzucht 50(1), (2007).
[4] HMT Boer, C Stötzel, S Röblitz, P Deuflhard, RF Veerkamp and H Woelders, J. Theor. Biol. 278, 20–31 (2011).
[5] C Stötzel, J Plöntzke, W Heuwieser, and S Röblitz, Theriogenology 78(7), 1415–1428 (2012).

III-40: *Sean Oosterholt* Model-based extrapolation and dosing recommendation for raxibacumab in children from birth to <18 years of age

Sean Oosterholt (1,2), Oscar Della Pasqua (2)
(1) Clinical Pharmacology & Therapeutics, UCL School of Life and Medical Sciences, London, UK, (2) GlaxoSmithKline, London, United Kingdom

Objectives: Raxibacumab is a fully humanised monoclonal antibody that blocks the protective antigen-receptor interaction of B. anthracis, thereby protecting target cells from PA binding to anthrax toxin receptors. Ultimately, this mechanism preserves host cells from anthrax toxin mediated effects. Raxibacumab, is currently approved in the USA for individuals exposed to inhaled anthrax, who are symptomatic of the infection. The aim was to review the dose rationale for raxibacumab in children taking into account the contribution of maturation and other age-related differences in drug disposition.

Methods: Rich pharmacokinetic data from three different trials in healthy adult subjects were analysed, yielding a pool of 322 subjects (age: 39 ±15, body weight: 76.9 ±117.4). The analysis was performed using a non-linear mixed effects modelling approach. Final parameter estimates were used to extrapolate drug disposition from adults to children. Simulation scenarios included the effect of changes in pharmacokinetics due to physiological growth, maturation and a combination of both factors. Predicted AUC, C_{max} and T $>C_{max}$ were used as parameters of interest for the purposes of this analysis. Dose recommendations for children from birth to < 18 years of age were derived taking into account the observed exposure to raxibacumab in adults and pre-clinical efficacy experiments.

Results: The PK of raxibacumab after intravenous administration of a 40 mg/kg dose was best described by a two-compartment model with first order absorption and elimination. There was no accumulation, metabolic inhibition, or induction observed during the course of treatment. Body weight was found to be a significant covariate on clearance, volume of distribution, inter-compartmental clearance and peripheral volume. Simulations showed that a combination of allometric scaling and maturation function reflected the most likely scenario in young children, with changes in drug disposition leading to an increase in drug levels > 2 times the maximum exposure observed in adults.

Conclusion: Given the nature of the infection, extrapolation is the only method available to explore the dose rationale for this vulnerable population. Extrapolations showed that the use of a weight-banded dosing regimen accounts for the most likely physiological changes in the disposition of raxibacumab, with doses ranging from 75 mg/kg in children with body weight < 1.5 kg to 40 mg/kg in patients with body weight > 50 kg.

III-41: *Stine Timmermann Ottesen* Analysing the contribution to receptor occupancy from active metabolites

Stine Timmermann, Dorrit Østergaard Nilausen and Johan Areberg
H. Lundbeck A/S

Objectives: To present a study design and modelling approach for investigating the contribution to receptor occupancy from active metabolites with longer terminal half-lives than the parent compound and to use model simulations to illustrate the utility of the approach.

Methods: Time-matched plasma concentrations of parent compound, its metabolite, and receptor occupancy data were obtained from 6 subjects in an open label, multiple dose positron emission tomography study. The subjects were dosed once daily for three weeks to obtain steady state of the parent compound. Three PET scans were performed after the last dose: At t_{max}, at one week, and at two weeks post the last dose, in order to obtain the largest difference between exposures of parent and metabolite. The PK/PD (occupancy) relationship was analysed by an E_{max} model using non-linear mixed effect modelling implemented in NONMEM 7.2.0 [1]. Plasma concentration of the metabolite was included in the model as a continuous covariate. The performance of the modelling approach was investigated by simulating different receptor-drug systems with varying contributions (receptor affinities) from the metabolite.

Results: The occupancy versus plasma concentrations data of the parent compound were adequately described by an E_{max} model with additive and proportional inter-individual variability on E_{max} and EC_{50}, respectively. The residual error model was additive. Including the metabolite plasma concentration data did not improve the model fit significantly. Simulations showed that the design of the study together with the modelling approach can detect contributions from the metabolite also when the metabolite has low receptor affinity compared to the parent compound.

Conclusions: The analysis of the receptor occupancy-PK data showed that the metabolite did not contribute significantly to the receptor occupancy. The simulations supported that the modelling approach can identify contributions to receptors occupancy from the metabolite even when the relative affinity of the metabolite is low.

References:

[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.

III-42: *Shan Pan* Delineation of the treatment effect of methotrexate when used in combination therapy for rheumatoid arthritis

Shan Pan (1), Lisa Stamp (2), Stephen Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin, New Zealand (2) Department of Medicine, University of Otago, Christchurch, New Zealand

Objectives: Rheumatoid arthritis (RA) is a chronic autoimmune disorder that is characterised by inflammation in joint synovial membrane [1]. For effective control of RA and hence the prevention of joint destruction, multiple drugs including the gold-standard treatment methotrexate (MTX) are used in routine clinical care. The objective of this study is to determine whether it is possible to delineate the treatment effect of MTX in the presence of other RA treatments under an observational cohort study using clinical trial simulation.

Methods: The Early Arthritis Observational Study at Christchurch Hospital was established in 2004. Data on treatment history and disease activity score in 28 joints (DAS28) were available for 146 patients. In total 14 RA treatments including MTX were used and categorised based on the onset of action (i.e. rapid, intermediate and delayed). Individual patients' treatment history in the observational study was extracted using MATLAB® (R2013b) and the time course of DAS28 was simulated based on the extracted treatment history. It was assumed that individual DAS28 ($DAS28_{ij}$) changed from the baseline ($DAS28_{\emptyset,i}$) due to both treatment effects (E_{ij}) and the natural history of disease (NH_{ij}) considering the measurement error (ε_{ij}), as given by

$$DAS28_{ij} = DAS28_{\emptyset,i} - E_{ij} + NH_{ij} + \varepsilon_{ij} .$$

Here subscripts i and j represent the jth clinical visit in the ith individual. E_{ij} is considered to be nonlinear and additive, and NH_{ij} is linear and symptomatic [2].

Model parameters were derived from the data, the literature and expert opinion. The simulation performance was evaluated using local polynomial regression (LOESS). Treatment effects of individual categories were explored under different study designs and were estimated through stochastic simulation-estimation in NONMEM® 7.2.

Results: The LOESS curves in both observed and simulated DAS28 profiles had similar trends after patients being stratified into high and low disease baseline groups. Under slow RA progression, parameters pertaining to RA treatment effects were precisely estimated. However, the rapid disease progression was found to confound the treatment effects irrespective of study design.

Conclusions: Under the observational study design, MTX treatment effect was able to be delineated when the RA disease progression was slow. In future, a more mechanistic approach using population kinetic-pharmacodynamic modelling may be developed to learn about the treatment effect and optimal doses of MTX.

References:
[1] Cohen S et al. Arthritis Rheum. 2002;46(3): 614-24.
[2] Holford N. Br J Clin Pharmacol. 2015;79(1): 18-27.

III-43: *Theodoros Papathanasiou* Population modelling of the synergistic effects of morphine and gabapentin in the rat: a response surface approach

Theodoros Papathanasiou, Rasmus Vestergaard Juul, Charlotte Gabel-Jensen, Anne-Marie Heegaard, Mads Kreilgaard and Trine Meldgaard Lund
Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen

Objectives: Combination of morphine and gabapentin has shown to be promising for managing postoperative pain [1]. Finding the right combination however has proven to be a challenge. PKPD modelling can be used to identify the optimal concentration-effect relationship of combinations.

Methods: In a blinded, randomized, 16 arms study, the pharmacokinetic (PK) and pharmacodynamic (PD) interactions of morphine and gabapentin were evaluated. In the plantar incision model in the rat [2], a series of blood samples and hind paw withdrawal thresholds, after subcutaneous administration of morphine (1, 3 and 7 mg/kg), gabapentin (10, 30 and 100 mg/kg) or their combination (9 combinations of the above doses) were obtained. Population PKPD modelling was performed in NONMEM 7.3 [3].

Results: Morphine and gabapentin distribution were best described with a three- and a one- compartment model respectively. No significant PK interactions were identified. Synergistic effects in the PD level were characterized using a response surface approach. Full reversal of withdrawal thresholds for the pain stimulation was estimated at a morphine plasma concentration of 1600 ng/ml. Co-administration of up to ~40 µg/mL of gabapentin led to reduction of the needed morphine plasma concentration down to 1300 ng/ml (~ 21% reduction).

Conclusions: The synergistic effects of morphine and gabapentin were well described using a response surface approach. This study highlights the importance of finding the right combination in multimodal analgesia and the developed model might help in guiding clinical studies for the selection of appropriate doses.

References:

[1] Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet [Internet]. Elsevier Ltd; 2011;377(9784):2215–25.
[2] Brennan TJ, Vandermeulen EP, Gebhart GF. Characterization of a rat model of incisional pain. Pain [Internet]. 1996 Mar;64(3):493–501.
[3] Beal S, Sheiner L, Boeckmann A, Bauer R. NONMEM user's guides. (1989-2009). Icon Dev Solut Ellicott City, MD, USA, 2009.

III-44: *Zinnia Parra-Guillen* Pharmacokinetic analysis of midazolam and caffeine as probe drugs for cytochrome phenotyping in erlotinib treatment

Zinnia P. Parra-Guillen (1), Markus Joerger (2), Benjamin Berger (3), Manuel Haschke (3), Charlotte Kloft (1)
Zinnia P. Parra-Guillen (1), Markus Joerger (2), Benjamin Berger (3), Manuel Haschke (3), Charlotte Kloft (1)

Objectives: Erlotinib is a tyrosine kinase inhibitor widely used in the treatment of non small-cell lung cancer. Similar to other molecules of this class, large inter-patient variability has been shown in clinical practice [1]. Erlotinib is mainly metabolised by CYP3A4 and to a lesser extent by CYP1A2, both enzymes varying largely across individuals. Therefore, enzymatic information could be used to individualise therapy and reduce variability. A prospective, nonrandomized, pharmacological cohort study was performed to assess the association between erlotinib exposure and cytochrome activity using midazolam and caffeine as probe drugs for characterising CYP3A4 and CYP1A2 phenotype, respectively (NCT01402089). The aim of this work was to describe the pharmacokinetics (PK) of the two probe drugs used in the study and their major metabolites (OH-midazolam and paraxanthine), as well as to develop the base model for erlotinib and its main metabolite, OSI-420.

Methods: Patients received erlotinib 150 mg orally once daily (n=36, dose reductions were allowed). Information regarding dosing times were extracted from the patients' dosing diaries. On day 1 and after an overnight fast, 2 mg oral midazolam and 100 mg oral caffeine after 36 h of abstinence were administered. Plasma samples for the probe drugs, erlotinib and the metabolites were collected after 1,2,3,4 and 6 h. Additional measurements of erlotinib and OSI-420 were available at steady-state. Data analysis was performed using NONMEM 7.3.

Results: Midazolam PK was best described with a 2 compartment disposition model, while caffeine and erlotinib were adequately described using a 1 compartment model. Due to the fast drug absorption of midazolam and erlotinib, this process could not be identified based only on the available data, and the absorption rate constants were fixed to the literature values of 3.18 [2] and 1.09 h-1 [3] respectively. Midazolam and erlotinib clearance were estimated to be solely dependent of metabolite formation (additional elimination was not identifiable). Finally, paraxanthine pharmacokinetics could not be characterised due to the short collection sampling times (only absorption phase).

Conclusions: Midazolam and caffeine probe drug PK have been adequately described. Different relevant metrics such as clearance, area under the curve or parent/metabolite ratio can be now computed and explored as potential covariates to explain inter-individual variability in erlotinib clearance.

References:
[1] H.J. Klümpen, C.F. Samer, R.H.J. Mathijssen et al. Moving towards dose individualization of tyrosine kinase inhibitors. Cancer Treatment Reviews, 37: 251-260 (2011).
[2] A. van Rongen, L. Kervezee, M.J.E. Brill et al. Population Pharmacokinetic Model characterizing 24-Hour Variation in the Pharmacokinetics of Oral and Intravenous Midazolam in Healthy Volunteers. CPT: Pharmacometrics Syst. Pharmacol., 4: 454-464 (2015).
[3] E. Petit Jean, T. Buclin, M. Guidi et al. Erlotinib: Another Candidate for the Therapeutic Drug Monitoring of Targeted Therapy of Cancer? A Pharmacokinetic and Pharmacodynamic Systematic Review of Literature. Ther. Drug Monit. 37: 2-21 (2015).

III-45: *Sophie Peigne* Optimal design in the analysis of a clinical study in paediatric population

Sophie Peigné, Sylvain Fouliard, Adrien Tessier and Marylore Chenel
Institut de Recherches Internationales Servier,

Introduction: A safety dose ranging study that included a 3 days treatment period with 7 PK samples collected each day was conducted in 51 paediatric patients with drug S (marketed in adult) with the objectives to build a population PK model in the paediatric population, to quantify the variability and identify the sources of variability and finally to compute derived secondary PK parameters in order to perform dose recommendation for the following phase III studies.

Methodology: During the paediatric development, a first step consisted in performing an identifiability analysis to evaluate whether the 2 compartmental model in adult population could be applied to the available paediatric data [1]. Then a population modelling approach was used to characterize the PK of drug S in the paediatric population and a covariate analysis was performed testing the covariates found in adult as a starting point and some well-known features of the paediatric population *i.e.* age and weight effect [2]. More specifically, an optimal-design based approach was used in order to assess whether the proposed study design with the number of subjects would allow the characterization of a gender effect, a covariate that was found in adult.

Finally, using the PK model developed, simulations were performed based on the assumption that the relationship exposure/efficacy was similar between adult and children population in order to perform dose recommendation.

Results: The data did not support any influential covariates, as opposed to the adult model. It was shown that a poor power was achieved if the magnitude of this effect was 2-fold for gender effect, and satisfactory for a 4-fold effect. However, the limitations of data that were available for the paediatric population analysis, questions the broader validity of covariate analysis.

The identifiability analysis based on simulations and design evaluation showed that the PK sampling times were unfortunately not optimized because of the high amount of BLQ and the data only supports a 1 compartment model.

Individual PK parameters derived from the final PK model were calculated at each dose. A direct comparison was performed with adult values and showed no difference between the two populations.

Conclusion: This model allowed to perform dosing recommendation for the next phase III study and will be further refined with the new data coming, especially regarding covariate effect assessment.

References:

[1] Retout S, Duffull S, Mentré F. Development and implementation of the population Fisher information matrix for the evaluation of population pharmacokinetic designs. Computer Methods and Programs in Biomedicine 2001; 65: 141-51.

[2] Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.

III-46: *Nathalie Perdaems* PK/PD modelling: a usefull tool to train people to better design in vivo chronic study in ob/ob mice

Nathalie Perdaems (1), Valérie Duvivier (2), Sylvain Fouliard (3), Marylore Chenel (4)
(1) Early PK and PKPD modelling, Technologie Servier, Orléans, France, (2) Metabolism, Institut de recherche Servier, Suresnes, France, (3) Early PK and PKPD modelling, Institut de recherches internationales Servier, Suresnes, France (4) Clinical PK and Pharmacometrics, Institut de recherches internationales Servier, Suresnes, France

Objectives: In preclinical research, pharmacokinetic/pharmacodynamic (PK/PD) studies are very often not enough discussed between pharmacologists and modellers before the pivotal *in vivo* study, and sometimes are poorly designed. This work is to make the pharmacologists, *in vivo* techniciens and project leader in research and development aware to PK/PD modelling.

Methods: Using separate studies (a PK study and a PD study), a PK/PD model was developed for a S compound in type 2 diabetes disease. A PK model was built to describe the PK of the S compound in ob/ob mice after a single oral administration. Then a PK/PD model was built, using simulated average plasma concentrations of the S compound in ob/ob mice after repeated oral administrations for 3 days. The limitations of this approach and the interest to have PK in the same studies as PD to well characterize the PK/PD relationship was discussed with people in charge of the project. Simulations were performed to show what could be done with a proper model [1]. Optimal sampling was used to choose the PK sampling times for the 28 days PKPD study in ob/ob mice: feasible designs were evaluated after an optimization step [2].

Results: Using the separate studies, a PK/PD model was built but some parameters were estimated with a relatively low precision of estimation (RSE% up to 140%). The PK of the S compound was assumed to be linear and the characterization of the respective PK and the PD variabilities was not possible, as PK was fixed, all the variability was estimated on PD. The optimized sampling times were 0.2, 1.8, 3.2, 5.2, 11.8 and 23.6 h. The interest to have sampling times after 6 h was confirmed by evaluating different experimental designs to improve the precision of estimated parameters. After discussion with the pharmacologists, the design of the 28 days PK/PD study was modified: sampling times for the PK analysis of the S compound in the 4 groups (with 4 different doses of S compound) and the two last sampling time were 8 h and 24 h.

Conclusions: Discussions between pharmacologists and modellers as early as possible in the preclinical development helps to better design PK/PD studies in order to well characterize the PK/PD relationship. To be part of the drug development at the beginning allows to propose a modelling strategy for the translational drug development from animal to human.

References:
[1] Phoenix, WinNonlin 6.3 (Pharsight)
[2] PopED lite (University of Uppsala, Sweden)

III-47: *Belén Pérez Solans* Markov model for tumor shrinkage effects of combination therapy in non-metastatic gastric cancer patients

Belén P.Solans (1, 2), Iñaki F. Trocóniz (1, 2)
(1) Pharmacometrics and systems pharmacology, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona, Spain; (2) IdiSNA Navarra Institute for Health Research, Pamplona, Spain

Objectives: To develop a population K-PD model for tumour shrinkage effects of first line treatment in patients with locally advanced gastric cancer patients from whom scarce ordered categorical were obtained.

Methods: Data were obtained from 115 patients with locally advanced gastric cancer treated at the University Clinic of Navarra. Patients were divided in two protocols, one consisting on the administration of 3-4 cycles of neoadjuvant chemotherapy (CT) followed by neoadjuvant radiotherapy (CRT) (protocol 1); and the other consisting only in neoadjuvant CT and surgery (protocol 2). Surgery was scheduled 4 to 6 weeks after the end of the neoadjuvant treatment. Tumor size (CT scans) was measured at diagnosis and once or twice during treatment and prior to surgery; an additional tumour related measurement was obtained from biopsy (anatomy pathology) at surgery. Cancer stage of each individual was set using the TNM classification following the American Joint Committee on Cancer guidelines. From modelling purposes the TNM classification was reduced to 0 = partial response (downstage), 1 = stable disease (no change in the stage) and 2 = disease progression (upstage). At time of diagnosis it was assumed that all patients were on disease progression. Data were analysed under the population approach with NONMEN 7.3. Response measurements were treated as ordered categorical data using logistic regression and considering the contribution of first order markovian features.

Results: Significant treatment effects could be identified using the proposed analysis approach (other attempts did not succeed in extracting drug effects). Including time delays in drug effects did not improve data description. Similarly, data suggested that the markovian features, but not the tumor stage at diagnosis played a significant role in treatment effects.

Conclusions: Routine clinical data in general, and in oncology in particular, are sparse and scarce and represent a challenge from the modelling perspective. Herein we show that expressing TN response data in terms of down-, up-stage, and no change represents an alternative to characterize drug effects using logistic regression. Our analysis showed that markovian features were present in our data.

III-48: *Alejandro Pérez-Pitarch* Empagliflozin as Adjunct to Insulin in Patients with Type 1 Diabetes Mellitus: Modelling Rate and Severity of Hypoglycemic Events

Alejandro Pérez-Pitarch
Boehringer Ingelheim Pharma GmbH

Objectives: Due to its insulin-independent mechanism of action, empagliflozin is under clinical investigation as adjunct to insulin to improve glycemic control in patients with type 1 diabetes mellitus (T1DM). A previous analysis of the EASE-1 trial (4-week, randomized, blinded, placebo-controlled trial of empagliflozin as adjunct to insulin in patients with T1DM) reported that rates of symptomatic hypoglycemia with plasma glucose

Methods: Hypoglycemic event (HYPO) data from the EASE-1 trial were analyzed. To describe the repeated time to events (RTTE), a parametric survival model was fitted to the data using NONMEM 7.3. To simultaneously capture the severity of events, the RTTE model was combined with an ordered categorical model to form the RTTCE model [2]. The influence of insulin titration, individual predicted empagliflozin AUCs at steady state (AUCss) and other patient-related covariates were explored. The performance of the model was evaluated with Visual Predictive Checks of the Kaplan Meier curves.

Results: Reporting-rates of asymptomatic and symptomatic HYPOs proved to have a different profile and thus, asymptomatic HYPOs were excluded from the analysis. The rate of symptomatic HYPOs was best described by a Gompertz model. The shape parameter proved to be influenced by insulin titration. When insulin was not titrated, instantaneous hazard increased over time, but once insulin was titrated and patients were stabilized, instantaneous hazard decreased over time. Higher empagliflozin AUCss were related to a lower HYPO risk. The hazard of having a symptomatic HYPO increased with lower mean glucose concentrations and female sex. The simultaneous description of rate and severity of events allowed identification of an inverse correlation between them.

Conclusions: The proposed model described the symptomatic HYPOs reported in the trial and provided information regarding patient- and study-specific factors influencing the risk of having a HYPO. This work represents a first exploratory step in the direction of a model-informed exposure-risk-benefit evaluation for empagliflozin as a treatment option in patients with T1DM, and will be further refined with availability of future data.

References:
[1] Pieber TR, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes Obes Metab. 2015; 17(10):928-35.
[2] Plan EL, Karlsson KE, Karlsson MO. Approaches to simultaneous analysis of frequency and severity of symptoms. Clin Pharmacol Ther. 2010; 88(2):255-9.

III-49: *Carlos Perez-Ruixo* Population pharmacokinetics and antiviral efficacy in neonatal lambs: evidence of rapid maturation and auto-induction drug effect in metabolic clearance

Carlos Perez-Ruixo (1), Peter Rigaux (1), Stefaan Rossenu (1), Juan Jose Perez-Ruixo (1), David Lançois (2), Mark Ackermann (3) and Dymphy Huntjens (1)
(1) Janssen R&D, Beerse, Belgium, (2) Janssen-Cilag, Val de Reuil, France, (3) Iowa State University, Ames, USA

Objectives: To develop a population pharmacokinetic model in neonatal lambs to describe plasma and lung concentrations of a new compound in development and determine its impact in lung infection.

Methods: Three groups of five lambs were inoculated with virus and doses of 2, 10 and 50 mg/kg of compound x were administered respectively. Blood samples were collected just before the first dose, at 2 hours after the first and the last dose and at 24 hours following each dose until 6th day. Lung concentrations were measured at sacrifice (day 6). A total of 112 plasma and 11 lung concentrations were obtained from the study. Pharmacokinetic data were analyzed with non-linear mixed effect model using NONMEM 7.3 software and model evaluations were performed using predictive checks and non-parametric bootstrap analysis.

Results: A one compartmental model with first-order absorption, asymptotic exponential maturation-increase in clearance (k_{mat}) [1] and enzyme auto-induction [2] drug effect was shown to adequately describe plasma pharmacokinetics. The auto-induction was described with an enzyme turn-over model in which the compound x plasma concentration increased the enzyme production rate (k_{enz}) in a linear fashion, where α was the linear relationship between the auto-induction effect and plasma concentrations. Lung pharmacokinetics was described using a general PBPK linear distribution model where the lamb physiological parameters were derived from the literature [3,4]. The estimated half-lifes for k_{mat} *and* k_{enz} were 6.31 days and 3.29 days respectively, while α was 0.094 mL/ng. Both, the maturation and auto-induction drug effect lead to a 1.79-fold increase in metabolic clearance in 6 days. The partition coefficient (k_p) [5] driving the drug uptake into the lung was estimated to be 0.68 identical to results reported in adult rats. Model-based simulations suggest that a 25 mg/kg can produce a 95% mean inhibition of lung infection after 6 days post inoculation of the virus in lambs.

Conclusion: The PK model developed in neonatal lambs, properly describes the concentration time course in plasma and lungs. Based on PK/PD modeling, compound x shows promising antiviral activity in lambs.

References:
[1] Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008; 48: 303-32.
[2] Clewe O, Goutelle S, Conte JE Jr, Simonsson US. A pharmacometric pulmonary model predicting the extent and rate of distribution from plasma to epithelial lining fluid and alveolar cells--using rifampicin as an example. Eur J Clin Pharmacol. 2015; 71: 313-9.
[3] Gratama JW, Dalinghaus M, Meuzelaar JJ, Gerding AM, Koers JH, Zijlstra WG, Kuipers JR. Blood volume and body fluid compartments in lambs with aortopulmonary left-to-right shunts. J Clin Invest. 1992; 90: 1745-52.
[4] Jani J, Breysem L, Maes F, Boulvain M, Roubliova X, Lewi L, Vaast P, Biard JM, Cannie M, Deprest J. Accuracy of magnetic resonance imaging for measuring fetal sheep lungs and other organs. Ultrasound

Obstet Gynecol. 2005; 25: 270-6.
[5] Thompson MD, Beard DA, Wu F. Use of partition coefficients in flow-limited physiologically-based pharmacokinetic modeling. J Pharmacokinet Pharmacodyn. 2012; 39: 313-27.

III-50: *Caroline Petit* Early phase dose-finding designs for bridging studies in pediatrics

Caroline Petit (1), Adeline Samson (2), Satoshi Morita (3), Jérémie Guedj (4), Vincent Julien (5), Emmanuelle Comets (4, 6), Sarah Zohar (1)?

(1) INSERM, UMRS 1138, CRC, Team 22, Univ. Paris 5, Univ. Paris 6, Paris, France ; (2) LJK, UMR CNRS 5224, Univ. J. Fourier, Grenoble, France ; (3) Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan ; (4) INSERM, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France ; (5) Pharmacology Department, Univ. Paris 5, Sorbonne Paris Cité, Inserm U1129, HEGP, Paris, France ; (6) INSERM, CIC 1414, Univ. Rennes 1, Rennes, France

Objectives: Dose-finding (DF) studies are challenging to calibrate, particularly in a paediatric population. Settings are usually chosen by usage or expert advice, without clear underlying methodology. We investigated calibrating an existing DF model for a paediatric population using adult observations, such as pharmacokinetics (PK), toxicity and efficacy, in order to choose (i) the parameters of the DF model, i.e. the initial guess of toxicity for each dose (working model WM) and the prior distribution of parameters, and (ii) the dose-range given to the paediatric population in the study. We evaluated the resulting method on a drug used against cancer, erlotinib.

Methods: Our approach relies on the bivariate continual reassessment method (bCRM) [1], which evaluates both efficacy and toxicity with a power model and a Bayesian estimation. For calibration, we assumed that target exposures, measured by AUC, were the same in both populations. We extrapolated paediatric clearance from the adult value by allometry and maturation [2, 3]. We obtained a paediatric model (bCRMpaed) by calibrating the WM assuming similar toxicities as those observed in adults. The variances of prior distributions were set using the ESS criterion [4]. We built a dose range based on extrapolation processes from adult doses with maturation and allometry. For comparison purpose, we also used a dose range with the current practice, that is a dose range linearly adjusted from adult dose on weight. The different approaches were compared in a simulation study aiming to design a DF study for the anticancer drug erlotinib in a population of children aged 2 to 5. Performances for each scenario were assessed by compting the percentage of simulated trials that selected the right dose.

Results: For erlotinib, the maturation and allometry dose ranges yielded doses different from the current practices. For every dose range, the bCRMpaed method selected the appropriate dose in a higher percentage of simulated datasets (10%-15%) than the bCRM. In scenarios where paediatric doses were different from adults (misspecification of bCRMpaed), results were similar to bCRM.

Conclusion: Designing a paediatric DF study based on former adult information can significantly improve the chance of selecting the appropriate dose for a drug in a paediatric population. Moreover, the use of extrapolation may improve the choice of evaluated doses in paediatrics.

References :

[1] Zohar S. and O'Quigley J. Identifying the most successful dose (msd) in dose-finding studies in cancer. *Pharmaceut. Statist.*, 5:187–199, 2006.

?[2] Anderson B.J. and Holford N.H.G. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug. Metab. Pharmacokinet.*, 24:25–36, 2009. ?

[3] Petit C., Jullien V., Samson A., Guedj J., Kiechel J.R., Zohar S., and Comets E. Designing a paediatric study for an antimalarial drug including prior information from adults. *Antimicrob. Agents Chemother.* Accepted

manuscript posted online 28 December 2015. ?
[4] Morita S., Thall P.F., Müller P. Determining the effective sample size for a parametric prior. *Biometrics,* 64 :595-602, June 2008.

Acknowledgment: Caroline Petit was supported during this work by a grant IDEX from the university Sorbonne Paris Cité (2013, project 24).

III-51: *Séverine Petitprez* Population pharmacokinetic meta-analysis of seven antiretroviral drugs

S. Petitprez (1), Y. Thoma (2), Y. Sutter (2), R. Hooper (2), M. Arab-Alameddine (3), T. Buclin (1), C.Csajka (1,4) and M. Guidi (1,4).

(1) Division of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland, (2) Reconfigurable and Embedded Digital Systems Institute, School of Business and Engineering Vaud, University of Applied Sciences Western Switzerland, Yverdon-les-Bains, (3) Merck Biopharma, Quantitative üharmacology-global Early development, Switzerland, (4) School of Pharmacy, Department of Pharmaceutical Sciences, University of Geneva and Lausanne, Geneva Switzerland

Objectives: The giant advances in antiretroviral therapy (ART) in the last two decades have transformed HIV infection from a deadly disease into a manageable chronic condition. In this context, therapeutic drug monitoring (TDM) has acquired increasing relevance in the optimization of dosage regimens. In this study, a systematic review of available population pharmacokinetic (Pop-PK) studies was performed in order to generate meta-models of seven different ART drugs. These models will be implemented into a Bayesian TDM software which is currently under development.

Methods: A systematic literature search of Pop-PK studies on seven ART drugs was conducted. Pop-PK parameters were retrieved and normalized for a typical individual (70 kg, male, Caucasian, carrying reference allele for all influencing genetic covariates). Each model was then reduced to a one-compartment model with first-order absorption and elimination, retaining inter-patient variability on the PK parameters and proportional error models for residual variability description. Summary pharmacokinetic parameters across all studies were calculated with R using random effects models. PK percentiles for standard dosage regimens were generated (NONMEM®). The validation of the meta-models was performed by calculating bias and precision between predicted and observed ART concentrations collected within the framework of the Swiss HIV Cohort Study (SHCS), as well as visual predictive checks (VPC).

Results: This study provides a concise summary of Pop-PK models and parameters of seven ART. Clearance (CL), central volume of distribution (Vz) and absorption rate constant (Ka) values could be extracted from all the studies. Individual and summary CL and Vz values were in good accordance among the studies except for darunavir where Vz values varied between the 2 publications. Ka values showed more variability. Adequate predictions of drug concentrations were obtained in the validation process for all ART drugs.

Conclusions: This study provides Pop-PK parameters across all available studies for seven different ART drugs. Combined with the use of an user-friendly and state-of-the-art TDM computer software, these results will provide a valuable tool for optimizing antiretroviral therapy based on best available evidence.

III-52: *Tatiana Petukhova* Population PK modeling of RPH-104, novel optimized IL-1 beta trap, and assessment of the immunogenicity effect on pharmacokinetics

Evgeny Metelkin (1), Tatiana Petukhova (1), Oleg Demin (1), Elena Shipaeva (2), Mikhail Samsonov (2), Anna Krotkova (2), Yan Lavrovsky (3)
(1) Institute for Systems Biology, Moscow, Russia, (2) JSC R-Pharm, Moscow, Russia, (3) R-Pharm Overseas, Inc., San Diego, USA

Objectives: RPH-104 (JSC R-Pharm) is a novel heterodimeric fusion protein, capable of inhibition of human IL-1 beta/IL-1F2 signaling pathway, for the treatment of autoimmune disorders associated with the overproduction of IL-1 beta cytokine (Behcet disease, FMF). The safety and PK of RPH-104 were assessed in studies on cynomolgus monkeys. The objective of this paper was to describe PK data in terms of population PK model and, in addition, to perform evaluation of immunogenic increase of elimination based on studies data in monkeys.

Methods: Based on PK monkeys data the population model was developed. Additional data of anti-drug antibody (ADA) production were used as categorical data (ADA-status) or as ADA levels in plasma to assess immunogenicity effect. The modeling and verification steps were performed in NONMEM V.7.3.0. FOCE method was used for estimations. Data processing and graphics were performed in R.

Results: Pharmacokinetics of RPH-104 in monkeys was described by 2-compartment model with linear elimination. Unexplained inter-individual variability was evaluated for parameters of central compartment volume and clearance. The parameter estimates of the model without effect of the immunogenicity were significantly biased. Implementation in model ADA production subject status in answer to RPH-104 therapy was allowed to decrease bias in parameter estimates. Model with effect of immunogenicity resulted in 5.5-fold increase of clearance following ADA response.

Conclusions: Population PK model of RPH-104 was developed. ADA production was describing as simple model with 5.5-fold increase of clearance following ADA response.

III-53: *Thomas Peyret* A mechanistic maternal-fetal growth energy budget model

Thomas Peyret (1), Samer Mouksassi (1) and Shasha Jumbe (2), representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community
(1) Certara Strategic Consulting, Montreal, QC, Canada, (2) Bill and Melinda Gates Foundation, Seattle, WA, USA

Background: Metabolic cost and metabolic consequences due to metabolic adjustments occurring during pregnancy and lactation to support fetal growth and milk synthesis are poorly understood.

Objectives: To develop a growth model of fetal weight based on fetus energy expenditure within a population approach modelling framework, in order to quantify required uniform flow of nutrients to the fetus and to the mammary gland, and the effect on maternal energy metabolism.

Methods: Daily energy deposition in a reference fetus was estimated by back calculating the necessary calories based on a published reference fetus mass growth equation[1]. Published energy densities of fat and fat free mass changes[2] and calculated fat and fat free masses based on literature data were used as energy sinks. Exponential, power, polynomial and Gompertz models were fitted to the cumulative energy deposition-gestational age (GA) curve and to the fraction of cumulative energy deposition in fat. Once the literature–based reference energy deposition curve was obtained, it was externally tested against ultrasound-based fetus and birth weight data from 1161 subjects [3] using a nonlinear mixed effects model estimating between-subject variability (BSV) on relevant parameters (FOCE-ELS engine in Phoenix® NLME™ v1.3,Certara, Princeton, NJ). Mother daily energy intake was estimated based on age, weight and height[2] and sex were also *a priori* included in the model as covariate.

Results: The piecewise equation for fat mass fraction consisted of three linear regressions for 0-25; 25-40 and > 40 weeks of GA. Gompertz equations obtained the best fitting performance for both cumulative energy deposition and its fat fraction. The energy-mass model predicted well the reference fetus weight-gestational age curve. The population model included BSV (<20%) on two parameters of the Gompertz model for cumulated energy deposition. Predicted individual fetal growth curve fitted well the trajectory of the observed fetus weight up to birth.

Conclusions: This study demonstrates the feasibility of using reverse engineering based on a closed model assumption of fetal caloric intake to predict fetus and birth weights.

Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative

References:
[1] Mikolajczyk et al. (2011) 377(9780):1855–1861.
[2] Hall et al. Lancet (2011) 378(9793):826-837.
[3] Soh et al. Int J Epidemiol (2014) 43(5):1401-1409.

III-54: *Kimba Eddy Phongi* Population Pharmacokinetics of the Novel Antimalarial OZ439

E.K. Phongi(1), M de Kock(1), L Wiesner(1), T. Wells(2), E. Decloedt(1, 3), K.I. Barnes(1), P. Denti(1).
(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; (2) Medicines for Malaria Venture, (MMV), Geneva Switzerland; (3) Department of Clinical Pharmacology, Stellenbosch University, Cape Town, South Africa

Objectives: OZ439 is a novel synthetic anti-malarial compound related to the artemisinin, but with a longer elimination half-life, which is being developed to be administered as part of a combination therapy for the cure of uncomplicated malaria [1]. The aim was to characterise the pharmacokinetics (PK) of escalating doses of OZ439 alone and in combination with mefloquine (one of the potential partner drugs studied) in healthy volunteers.

Methods: Two cohorts of South African healthy adult volunteers received respectively 100 mg and 400 mg single doses of OZ439 [2]. All volunteers were studied over two periods, the first period evaluated OZ439 alone, and the second period in co-administration with mefloquine. Cohort 1 had 12 volunteers and Cohort 2 has 18 volunteers. During period 1 venous blood samples were collected pre-dose and at 1, 2, 3, 4, 6, 8, 10, 16, 24, 36, 48, 72, and 96 hours post-dose. During period 2, additional samples were collected also on day 8, 11, 15, 28 and 35 post-dose. NONMEM 7.3 with FOCE-I was used to analyse the PK data. Allometric scaling [3] was used to account for the effect of body size, using different predictors such as fat-free mass (FFM), fat mass and total weight. Data below the limit of quantification was imputed with half the value of low limit of quantification, and only the first values in a series was retained in the analysis.

Results: A three compartment disposition model with 1st-order elimination and transit compartment absorption fitted the data well. Scaling for FFM improved the estimation of clearance (CL), while body fat was the best predictor for the size of the larger peripheral compartment. The model estimated the typical value of CL to be 85 L/h. The data displayed a dose-exposure nonlinearity with higher exposures observed with increasing dose. No significant drug-drug interaction with mefloquine was detected

Conclusions: We described the PK of OZ439 and found that distribution is affected by body fat. The more-than-proportional increase in exposure with higher doses points towards probable saturation of metabolism or transporters. Integration of metabolite concentrations in the model may help elucidating this.

References:
[1] J. J. Moehrle, S. Duparc, C. Siethoff, P. L. M. van Giersbergen, J. C. Craft, S. Arbe-Barnes, S. A. Charman, M. Gutierrez, S. Wittlin, and J. L. Vennerstrom, “First-in-man safety and pharmacokinetics of synthetic ozonide OZ439 demonstrates an improved exposure profile relative to other peroxide antimalarials,” *Br. J. Clin. Pharmacol.*, vol. 75, no. 2, pp. 535–548, 2013.
[2] K. I. Barnes, “A phase I healthy volunteer study investigating the safety , tolerability & pharmacokinetics of co-administered single doses of OZ439 and mefloquine.,” 2012.
[3] B. J. Anderson and N. H. G. Holford, “Mechanism-based concepts of size and maturity in pharmacokinetics.,” *Annu. Rev. Pharmacol. Toxicol.*, vol. 48, pp. 303–332, 2008.

III-55: *Chiara Piana* A novel model-based methodology for the evaluation of abuse potential

Chiara Piana (1), Shaonan Wang (1), Roberta Bursi (1)
(1) Grunenthal GmbH, Aachen, Germany

Objectives: A modelling and simulation analysis has been performed to evaluate the potential correlation between plasma concentrations and abuse-related effects for a reference drug in comparison with a drug with a high abuse potential profile. The primary endpoint for the abuse-related effects was drug liking "at this moment" measured using a Visual Analogue Scale (VAS).

Methods: Given the distribution of the data, VAS for drug liking "at this moment" was considered as an ordered categorical variable and the scores were binned in three categories (drug disliking, neutral effect, drug liking). A population pharmacokinetics/pharmacodynamics (PK/PD) analysis was performed using a nonlinear mixed-effects approach as implemented in NONMEM 7.2. The final model was selected according to graphical and statistical criteria. After validation of model stability and predictive power, the final PK/PD model was used to predict the mean time-varying probability of drug liking after the administration of hypothetical doses of the reference drug.

Results: A logit model fitted adequately the data and an E_{max} model best described the correlation between plasma concentrations and drug effect for the reference drug and for the drug with high abuse potential profile. Model-based simulations indicated that in order to reach the same probability of drug liking as the drug with high abuse potential, the reference drug needs dosing higher than the limit of tolerability currently observed.

Conclusions: A novel model-based methodology has been developed to identify a concentration/drug liking correlation and to predict the mean time-varying probability of drug liking after the administration of hypothetical doses of a reference drug. Our investigation shows that modelling and simulation could successfully support the evaluation of abuse potential.

III-56: *Philippe Pierrillas* From mouse to human: comparison of interspecies translational strategies using integrative semi-mechanistic PK-PD models and PBPK-PD modeling to forecast efficacious clinical dose

Pierrillas Philippe (1), Hénin Emilie (1), Chenel Marylore (2), Amiel Magali (3), Bouzom François (3), Tod Michel (1)
(1) Université Claude Bernard, Lyon, France ; EMR 3738 Ciblage Thérapeutique en Oncologie, (2) Clinical Pharmacokinetic Department, Institut de Recherches Internationales Servier, Suresnes, France, (3) Technologie Servier, Orléans, France

Objectives: Bridging the gap between preclinical and clinical settings by anticipating human efficacy could be promising to improve drug development. This work focused on strategies based on modeling of preclinical data to anticipate human behavior of a new pro-apoptotic *S* compound.

Methods: Data from *in vitro* assays, PK, biomarker and tumor growth inhibition (TGI) studies in mice were considered. PK and response data from a phase 1 trial were collected (8 dose levels). Based on semi-mechanistic PK-PD models in mice and PBPK extrapolation, several PD extrapolation strategies were elaborated:

- Rocchetti approach (ROC) [1]
- Orthogonal Rocchetti approach (oROC) modifying the original ROC using an orthogonal regression
- Consistent across species approach (CAS) bringing out an efficacy parameter assumed consistent across species

Scaling species-specific parameters approach (SSP) assuming the concentration-TGI link is the same in mice as in humans, provided allometric scaling.

Results: *S* PK was best described by a 2-compartment disposition model with both saturable absorption and elimination. Tumor growth was modeled by a Koch model [2] inhibited by an all-or-none effect of caspase, defining a plasma concentration threshold for apoptosis, C_{THRE}. An hybrid PBPK approach [3] was applied to extrapolate the nonlinear PK and was well qualified on rat and dog data. Human observations were well predicted. oROC gave similar fitting performances as ROC on the 10 drugs from the original work [1]. ROC and oROC predict respectively a *S* clinical dose of 1470 and 2020mg. CAS was built on a relationship between TGI and the time that concentration remains above C_{THRE}, assumed to be consistent across species as time above Minimal Inhibitory Concentration and therapeutic efficacy for antibiotics [4-6]. Simulations with a *negligible natural tumor growth* assumption revealed a median response about 65% at 900mg whereas a *mice-equivalent natural tumor growth* assumption led to a median response of 23% at 900mg. SSP predicted a dose of 700mg to get a median response of 60%.

Conclusions: While empirical methods only predict a dose level, results of mechanism based strategies are preliminary and do not seem to be invalidated: proportion of patients responding to treatment is increasing with the dose while patients can respond from the first dose level. Those strategies seem to be more informative for the follow-up of a clinical study, highlighting the potential interest of such approaches.

References:
[1] Rocchetti M, Simeoni M, Pesenti E, De Nicolao G, Poggesi I (2007) Predicting the active doses in humans from animal studies: a novel approach in oncology. Eur J Cancer 43 (12):1862-1868. doi:S0959-

8049(07)00380-2 [pii] 10.1016/j.ejca.2007.05.011
[2] Koch G, Walz A, Lahu G, Schropp J (2009) Modeling of tumor growth and anticancer effects of combination therapy. Journal of pharmacokinetics and pharmacodynamics 36 (2):179-197. doi:10.1007/s10928-009-9117-9
[3] Sayama H, Komura H, Kogayu M, Iwaki M (2013) Development of a hybrid physiologically based pharmacokinetic model with drug-specific scaling factors in rat to improve prediction of human pharmacokinetics. Journal of pharmaceutical sciences 102 (11):4193-4204. doi:10.1002/jps.23726
[4] Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26 (1):1-10; quiz 11-12
[5] Andes D, Marchillo K, Stamstad T, Conklin R (2003) In vivo pharmacodynamics of a new triazole, ravuconazole, in a murine candidiasis model. Antimicrob Agents Chemother 47 (4):1193-1199
[6] Craig WA, Andes D (1996) Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 15 (3):255-259

III-57: *Teun Post* Application of a Shiny Workflow in Cardiovascular Effects Evaluations

Teun M. Post (1,2), Nelleke Snelder (1), Richard Hooijmaijers (1)
(1) LAP&P Consultants BV, Leiden, The Netherlands; (2) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden, The Netherlands

Objectives: The objective was to develop a workflow in which established and experimental treatment effects (structure and data) can be compared and therefore discussed within a team setting to support decision-making.

Methods: A Shiny application [1,2] provides an easy-to-generate and easy-to-use interface to visualize models in R, for instance to present its structure, and to compare model outcomes and observed data.

A previously reported preclinical Cardiovascular Effects Systems Pharmacology framework [4,5] was transformed from NONMEM to R [3] with an in-house developed R package, and implemented in Shiny. The framework contains several library compounds (e.g., propranolol, amlodipine) with their PK and corresponding effects on mean arterial blood pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR), and stroke volume (SV). The corresponding observed preclinical data was added to the application.

An option was incorporated to interactively visualize the output of new treatments based on its experimental or anticipated PK and PD characteristics, including the possibility to investigate a site of action and a type of exposure-response function. The outcome of the effects could be overlaid and combined, also with available observations.

Results: The user can:

1. Select a library model
    - Select dose/dosing regimen
    - Display the model structure and selected site of action
    - Plot its PK and PD
    - Overlay with observations or combine with other treatments
2. Select experimental PK and PD properties
    - Select site of action
    - Select type of exposure-response function
    - Select dose/dosing regimen
    - Select rat strain
    - Overlay with observations or combine with other treatments
    - Change PK and/or PD characteristics based on discussions or known properties (automatic update to outputs)
3. Upload additional data
4. Selection of plot types, layout and simulation characteristics
5. Save and export results for reporting or re-use

Conclusions: The workflow provided a means to 1) visualize complex systems pharmacology model structures, 2) compare treatment effects and observations, 3) enable team discussions (“what-if” questions), and 4) support decision-making within a broader team. Due to the modular setup of the

application, it can be extended to include items like additional treatment effects, data, and even analysis workflows (e.g. optimize selected model structures in NONMEM), and it can easily be converted to use within different projects.

References:

[1] *RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/*
[2] http://shiny.rstudio.com/
[3] R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/
[4] Snelder N, et al., Mechanism-based PKPD modeling of cardiovascular effects in conscious rats – an application to fingolimod, PAGE 22 (2013) Abstr 2686 [www.page-meeting.org/?abstract=2686]
[5] Snelder N, et al., Drug effects on the CVS in conscious rats: separating cardiac output into heart rate and stroke volume using PKPD modelling. Br J Pharmacol. 2014 Nov;171(22):5076-92

III-58: *Manuel Prado-Velasco* Bridging the gap between open and specialized modelling tools in PBPK/PK/PD with PhysPK/EcosimPro modelling system: PBPK model of methotrexate and 6-mercaptopurine in humans with focus in reusability and multilevel modelling features

Manuel Prado-Velasco
EcosimPro/PhysPK Unit, Empresarios Agrupados Internacional, Spain

Objectives: To validate a novel modelling and simulation biomedical tool, PhysPK/EcosimPro, through the building of a MTX and 6-MP PBPK model using a technique that promotes the reuse of models with different description scales (from group of cells to group of tissues).

Methods: A PBPK model for MTX and 6-MP, including stomach, gut lumen, liver, and kidney tissues with different modelling approaches (perfused limited and membrane limited), and description scales (kidney described through glomerulus' dynamics), has been built using the novel PhysPK/EcosimPro M&S tool [1]. The model was previously developed and validated in adults and children by Ogungbenro et al. [2-3], and considers enterohepatic flow, non-linear binding, and inhibition of 6-MP first-pass effect by MTX.
PhysPK/EcosimPro is a new M&S software for physiological and therapeutic systems that combines cutting-edge methodologies and technologies to provide:
• Specialized pre-built and protected extended PBPK/PK/PD human and animal models and devices models
• Independence of physiological model formulation from algorithmic issues
• Open GUI environment to build multi-level models according to a three-layer architecture for mechanisms, physiological / machine elements, and signal processing elements
These features are the basis for reusing models by adding or substituting mechanisms and subsystems at different levels.
The cited model has been built with PhysPK from scratch, and from Bischof et al. model [4], modifying several mechanisms, and tissues.
The model is finally extended to include a high-flux dialysis membrane connected to a patient. High MTX infusion doses followed by high-flux dialysis is performed in the model and compared with published results [5].

Results: Concentration-time profiles agree with those published in [2-3]. The extended model reproduced the behavior of MTX concentration for pediatric patients submitted to dialysis (F-40 and F-80 Fresenius membranes) [5]. The model building methodology and technology based on PhysPK/EcosimPro has been successfully validated.

Conclusion: Reusability and multilevel modelling have been successfully tested in PhysPK/EcosimPro through the development of a PBPK model for MTX and 6-MP. This software tool combines a non-algorithmic and object-oriented modelling methodology with a three-layer specialized biomedical modelling architecture to fill the gap between current open and specialized commercial modelling tools in this arena.

References:
[1] M. Prado-Velasco, "PhysPK/EcosimPro: Sistema de modelado y simulación de sistemas fisiológicos. Metodología, arquitectura y aplicación a problemas PBPK/PK/PD," in VI Jornadas de Modelización y Simulación en Biomedicina, 2015, p. 15.

[2] K. Ogungbenro and L. Aarons, “Physiologically based pharmacokinetic modelling of methotrexate and 6-mercaptopurine in adults and children. Part 2: 6-mercaptopurine and its interaction with methotrexate,” J. Pharmacokinet. Pharmacodyn., vol. 41, no. 2, pp. 173–185, 2014.
[3] K. Ogungbenro and L. Aarons, “Physiologically based pharmacokinetic modelling of methotrexate and 6-mercaptopurine in adults and children. Part 1: Methotrexate,” J. Pharmacokinet. Pharmacodyn., vol. 41, no. 2, pp. 159–171, 2014.
[4] K. B. Bischoff, R. L. Dedrick, D. S. Zaharko, and J. a Longstreth, “Methotrexate pharmacokinetics.,” J. Pharm. Sci., vol. 60, no. 8, pp. 1128–1133, 1971.
[5] J. M. Saland, P. J. Leavey, R. O. Bash, E. Hansch, G. S. Arbus, and R. Quigley, “Effective removal of methotrexate by high-flux hemodialysis,” Pediatr. Nephrol., vol. 17, no. 10, pp. 825–829, 2002.

III-59: *Tim Preijers* In silico evaluation of limited blood sampling strategies for individualized recombinant factor IX prophylaxis in hemophilia B patients

T. Preijers (1), H.C.A.M. Hazendonk (2), K. Fijnvandraat (3), F.W.G. Leebeek (4), M.H. Cnossen (2), R.A.A. Mathôt (1) for "OPTI-CLOT" working group.

(1) Hospital Pharmacy-Clinical Pharmacology, Academic Medical Center Amsterdam, the Netherlands. (2) Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital Rotterdam, the Netherlands; (3) Department of Pediatric Hematology, Academic Medical Center Amsterdam, the Netherlands; (4) Department of Hematology, Erasmus University Medical Center Rotterdam, the Netherlands.

Objectives: This *in silico* simulation study aims to develop limited sampling strategies (LSSs) for recombinant factor IX (rFIX) concentrate and to evaluate their predictive performance regarding the number and timing of blood samples.

Methods: A Monte Carlo (MC) simulation was performed to obtain 5000 full concentration versus time profiles using population PK parameters for rFIX from literature [1]. Eleven LSSs were developed with 1-3 samples taken in the 80-hour interval following administration of 100 IU/kg, from which four LSSs contained blood sampling within one day. The predictive performance of the LSSs was evaluated by comparing the empirical Bayesian estimates of PK parameters with the MC simulated values. The relative mean prediction error (rMPE%) and relative root mean squared prediction error (rRMSE%) were used to describe bias and precision, respectively.

Results: For each LSS bias was low for clearance (range -1.4% to +1.3%), terminal elimination half-life (range -1.7% to +0.5%) and steady-state volume of distribution (range -3.1% - +0.7%), whereas for predicted trough concentration at day 3 bias ranged from -1.6% to 11.2%. Precision of these parameters ranged from 6.5% to 12.8%, from 11.4% to 15.6%, from 9.5% to 20.7%, and from 21.1% to 53.7%, respectively. Predictive performance of the LSS with samples taken post-infusion and two samples on day 2 after administration was superior to the other LSSs.

Conclusions: This study demonstrates that LSSs can be developed by *in silico* simulation and evaluated for the individualized dosing of rFIX in severe hemophilia B patients. Simulations have an important additional value when designing clinical studies to evaluate LSSs in these patients.

References:

[1] Björkman S. Population pharmacokinetics of recombinant factor IX: implications for dose tailoring. Haemophilia : the official journal of the World Federation of Hemophilia. 2013; 19: 753-7.

III-60: *Claire Pressiat* Population pharmacokinetics of cotrimoxazole In West African HIV-infected children

Claire Pressiat
University Paris 5

Objectives: The aims of this study were to describe the pharmacokinetics of the cotrimoxazole (CTX : association of sulfamethoxazole (SMX) and trimethoprim (TMP)) in a large population of children, to identify factors influencing the pharmacokinetics of TMP and SMX, and to evaluate the doses recommended by the World Health Organization during childhood.

Methods: All HIV-infected children diagnosed before two years of age, and confirmed by DNA-PCR were enrolled in an initial therapeutic cohort offering a cART with cotrimoxazole prophylaxis (TMP/SMX: 200/40/day once daily) in Ouagadougou (Burkina Faso) and Abidjan (Ivory Coast). Quantification of TMP and SMX in human plasma collected 6 months, 19 months and 25 months after cART initiation was performed using a validated liquid chromatography method with UV-detector. Plasma concentrations collected from HIV-infected children aged from 6 months to 4 years were analyzed using a nonlinear mixed effects modeling, with NONMEM software. Estimated individual PK parameters were used to calculated individual exposures to TMP and SMX. Moreover, pharmacogenetics studies were carried out on the enzymes involved in the metabolism of SMX.

Results: Overall, 114 children with a median age of 1.8 years, a median weight of 8.9 kg, and a sex ratio (M/F) of 1.15 were analysed. TMP's and SMX's PK were described by a one-compartment model with first-order absorption and elimination. The effect on body weight on the apparent volume of distribution was significant for SMX and TMP. For the SMX, the effect of polymorphism of the enzyme NAT 1, involved in the metabolism of SMX, affects the clearance of the drug.

Conclusions: A very large interindividual variability in cotrimoxazole concentrations was pointed out. With the dosing regimen currently recommended, exposures are much lower of the children than those found in adults. In order to maintain a comparable exposure as in adults in this population, an increase of the dose should be considered.

III-61: *Angelica Quartino* Comparisons of Multiple Exposure-Response Methodologies in Oncology

Dan Polhamus (1), Jonathan French (1), Shang-Chiung Chen (2), Bei Wang (2), Chunze Li (2), Dan Lu (2), Sandhya Girish (2), Jin Jin (2), Angelica Quartino (2)
1 Metrum RG, Tariffville, CT; 2 Genentech, San Francisco, CA

Objectives: Exposure-Response assessment in oncology is complicated by many factors, e.g. alternate dosing history. In addition, for monoclonal antibodies (mAbs) exposure is confounded by key prognostic factors for the disease. M&S exposure-response (ER) analysis focuses on direct or indirect (e.g., via tumor growth inhibition (TGI)) ER for progression free survival (PFS) and overall survival (OS). Here, we compare different aspects of multiple direct ER methods, with a case example in oncology.

Methods: Direct ER methods were compared using data from an oncology Phase 3 trial: 1) stratified Kaplan-Meier (KM) estimates by exposure quartiles, 2) Cox proportional hazards (CPH) analysis with covariate adjustment by exposure quartiles or as a continuous function, 3) case matching (CM) to address confounding effects on ER by exposure quartiles, and 4) parametric survival modeling (PS) using covariate adjustment and longitudinal exposure to account for alternate dosing history and for extrapolation to other dosing regimens.

Results: KM, while easy to interpret and vizualize, don't account for confounding prognostic. Confounding factors are addressed with CPH, however it relies on assumptions about the relationship of covariates with outcome and the summary exposure metric. Case matching methods has recently been proposed by FDA to ease these assumptions [1], but ER assesment is no longer directly addressed as in the same manner as in CPH. A doubly robust ER using CPH within CM on strata of exposure is demonstrated, guarding against either poor matching or model misspecification. PS with covariate adjustments offers a direct longitudinal ER method, to complement indirect TGI methods. While TGI is a more mechanistic approach, PS may be preferred in cases where the tumor dynamics of the target leasions cannot fully predict survival due to e.g. new leasions and micrometastases. Longitudinal approaches has the advantage of directly accounting for alternate dosing history compared to ER methods that use summary exposure metrics, and allows for simulation of other dosing regimens.

Conclusions: Several direct methods for ER analysis are available. Here, we evaluate direct ER methods and propose a M&S strategy that is fit for purpose and provides a clear strategy for dose optimization if indicated, and addresses regulatory review questions.

References:
[1] Yang J, et al. J Clin Pharmacol. 53(2): 2013

III-62: *Rose Rachel* Development of a novel multi-compartment granuloma model to predict local drug distribution and its impact on pharmacodynamics and disease progression in tuberculosis.

Rachel H. Rose (1), Lu Gaohua (1), Janak Wedagedera (1), Ben G. Small (1), Adrian Barnett (1), Klaus Romero (2), David Hermann (3), Iain Gardner (1), Masoud Jamei (1).
(1) Simcyp (a Certara Company), Sheffield, UK (2) Critical Path Institute, Tuscon, AZ (3) Certara, Princeton, NJ, USA

Objectives: One of the hallmarks of pulmonary tuberculosis (TB) is the formation of granulomas, heterogeneous lesions composed of macrophage and neutrophil rich peripheral regions and a necrotic core, in the lungs of the infected host. Anti-TB drugs must penetrate these lesions to exert their effects. This work aimed to extend a permeability-limited lung model [1] to describe drug disposition within a tuberculosis granuloma and to incorporate a disease progression model that describes the growth of the granuloma and the pharmacodynamic effect of locally-acting drugs on bacteria located within different lesions of the granuloma.

Methods: A permeability-limited lung model was extended with the addition of a novel multi-compartment granuloma model consisting of three layers: the well vascularised cellular rim, the outer caseum and the inner caseum compartments. The rim was further sub-divided into mass, interstitial fluid (ISF) and blood compartments. Granuloma growth and disease progression in active and latent tuberculosis was modelled based on work published previously [2]. The volume of the rim mass compartment was defined by the total number of macrophages from the disease progression model and drug effects are incorporated as a local concentration dependent kill rate for bacteria localised to different compartments of the granuloma. The model has been implemented in Simcyp V16, with the disease progression model implemented via a Lua script to allow the user the flexibility to customise the model.

Results: Local free drug concentration within different granuloma compartments is dependent on the interplay between several factors including free drug concentration in the plasma and lung tissue of the simulated individual, active transport and passive permeability between granuloma compartments and binding within different compartments of the granuloma model. Local free drug concentration significantly impacts on the rate of killing of bacteria within different granuloma compartments and hence the predicted response to treatment.

Conclusions: The multi-compartment granuloma model provides a framework for investigating the impact of inter-individual variability in drug pharmacokinetics and local drug concentration on the killing of *M. tuberculosis* sub-populations. Ongoing work aims to validate the model predictions for anti-TB drugs and treatment regimens.

References:
[1] Gaohua L, Wedagedera J, Small BG, Almond L, Romero K, Hermann D, Hanna D, Jamei M, Gardner I. Development of a multicompartment permeability-limited lung PBPK model and its application in predicting pulmonary pharmacokinetics of antituberculosis drugs. CPT Pharmacometrics Syst Pharmacol (2015) 4(10):605-13
[2] Sud D, Bigbee C, Flynn JL and Kirschner DE. Contribution of CD8+ T cells to control of Mycobacterium tuberculosis infection. J Immunol (2006) 176**:**4296-314

III-63: *Christian Radke* Development of a PBPK approach to predict the pharmacokinetics in patients with sepsis

Christian Radke (1), Dagmar Horn (2), Christian Lanckohr (3), Michaela Meyer (4), Thomas Eissing (4), Georg Hempel (1)

(1) Department of Pharmaceutical and Medicinal Chemistry, Clinical Pharmacy, Westfälische Wilhelms-Universität Münster, Germany, (2) Department of Pharmacy, University Hospital of Münster, Germany, (3) Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital of Münster, Germany, (4) Systems Pharmacology CV, Bayer Technology Services GmbH, Leverkusen, Germany

Objectives: Sepsis is characterized by an excessive release of inflammatory mediators substantially affecting body composition and organ function further augmented by intensive care management (e.g. extensive fluid administration, administration of vasoactive drugs). Thus, drug pharmacokinetics can be altered resulting in uncertainty of pharmacotherapeutic success. Using vancomycin as a renally cleared model drug, a physiologically based pharmacokinetic (PBPK) model for septic patients was developed taking disease related physiological changes into account.

Methods: An extensive literature search was conducted to determine qualitative and quantitative information on physiological alterations described for different septic states and defined according to the official international guideline [1]. Gathered information was consolidated and informed patho-physiological parameter changes were incorporated in the PBPK software PK-Sim® [2], scaling a validated vancomycin model of healthy subjects. Furthermore, an individualized model approach was applied taking readily available patient characteristics into account, such as creatinine clearance (CrCL). Plasma concentrations for model validation, as well as individual patient characteristics were obtained from an ongoing prospective observational study at the University Hospital of Münster.

Results: Literature search yielded more than 100 studies, presenting information on various physiological parameters. However, quantitative data on some parameters are almost entirely lacking (e.g. metabolic enzyme activity, renal blood flow). The literature-based sepsis PBPK model showed a slight improvement when compared to a model considering no physiological alterations, with 59.3% vs 55.6% of the predicted values being within 30% of the observed values. The mean absolute prediction error (MAPE) was 38.0% vs 39.2%, respectively. However, a distinct improvement of the literature model was observed for higher concentrations during the distribution phase. Further individualization of the model significantly improved model performance, with the individualized model showing the best results with 88.9% of all predicted values being within 30% of the observed values and a MAPE of 17.6%.

Conclusions: Available literature information on physiological changes in sepsis improves model prediction regarding vancomycin distribution. For precise predictions in septic patients, individual patient characteristics such as CrCL are required.

References:

[1] Bone, R.C., et al., *Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine.* Chest, 1992. **101**(6): p. 1644-55.

[2] Eissing, T., et al., *A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks.* Front Physiol, 2011. **2**: p. 4.

III-64: *Christian Hove Rasmussen* Automated modeling workflow with LaTeX: from analysis to report

Christian Hove Rasmussen (1), Kaori Ito (1), Lynn McFadyen (1), Paula Burger (1), Mike K. Smith (1)
(1) Pfizer, Inc. Groton, CT, USA and Sandwich, Kent, UK

Objectives: The creation of a large report related to a quantitative analysis is often a painstaking and error-prone task, involving hours of manually copying and pasting figures into word processors, transcribing numbers into table cells, etc. Moreover, should the report require updates due to reviewer's comments or if the analysis needs to be rerun (e.g. due to a data update), the entire procedure needs to be redone and the resulting report subject to further quality control (QC).

Methods: In this poster we present an ongoing effort at Pfizer, Inc. to make reporting simple, reproducible, and user-friendly by utilizing an automated setup of modeling and data analysis combined with the document system LaTeX. The latter is customized to fit the needs of the pharmaceutical industry.

Results: The LaTeX system allows the user to create a publishable PDF document directly from figure image files and tables from CSV text files. This greatly simplifies formatting which is taken care of automatically according to a predefined template. The template has all submission-ready standards built into it and is therefore fully compliant with regulatory expectations. Furthermore, numbering of and references to sections, figures, tables, etc. is automatically updated as the document is written, and citations are loaded directly from e.g. Google Scholar or Medline using the LaTeX-based reference manager JabRef. The time required to create the report is reduced from weeks to days, and updating it to a matter of minutes or hours. This saves crucial time especially if rework is required in the final stages before a regulatory submission. The way we have set it up allows getting started with the document system with no prior knowledge of LaTeX and only a few hours of training.

Conclusions: Using the reproducible research methods above reduces the overhead in creating reports to the required standards; reduces the likelihood of manual transcription errors and focusses QC on technical and scientific issues rather than document preparation issues.

III-65: *Isabel Reinecke* Changes in endogenous estradiol concentrations explain fluctuations in levonorgestrel (LNG) concentrations during continuous treatment with LNG releasing intravaginal rings

Isabel Reinecke (1), Rüdiger Nave (2), Marcus-Hillert Schultze-Mosgau (2), Heinz Schmitz (3), Bart Ploeger (1)

(1) DD Clinical Pharmacometrics; (2) DD Clinical Pharmacokinetics; (3) Development Gynecologic Therapies; (1)-(3) Bayer Pharma AG, Berlin, Germany

Objectives: During treatment with low-dose levonorgestrel (LNG) for contraception in clinical phase I studies, fluctuations over time were observed in LNG plasma concentrations which cannot be described with help of the product's release profile and PK model. These fluctuations were even more distinct for the PD parameter serum sex hormone binding globulin (SHBG) which interacts with LNG. Endogenous estradiol (E2) concentrations are positively correlated with SHBG concentrations in premenopausal women [1]. However, fluctuations in LNG concentrations during treatment with low-dose LNG containing contraceptives as a result of these interactions have not been well described. The goal of this analysis was to describe the PK of LNG in a phase I study investigating LNG releasing intravaginal rings (IVRs) and in particular to explain the fluctuations in the LNG concentrations.

Methods: The pharmacokinetics (PK) of LNG was assessed in an open-label phase I study where the use of LNG releasing IVRs in dose range of 20 to 40µg/d was investigated over 56 days, ring change after 28 days, in 66 healthy young women by developing a population PK model using NONMEM (version 7.2.0). In order to describe the fluctuations, the assumption that E2 has an effect on SHBG was considered by including E2 measurements as covariate in the model.

Results: The PK of LNG was described by a two-compartment model including the interaction of LNG and SHBG where a turnover model for SHBG was used. SHBG concentrations followed the observed increase and decrease in E2 concentrations shortly thereafter indicating that E2 has a stimulating, delayed effect on SHBG concentrations, with higher E2 concentrations resulting in a stronger effect. Including the E2 effect on the SHBG synthesis in the model led to a better description of the PK of LNG and in particular of the fluctuations in the LNG and SHBG concentrations.

Conclusions: The PK of LNG was well described by the population PK model where the interaction of LNG and SHBG was considered and additionally a stimulating effect of E2 on the synthesis of SHBG was assumed. Comparison of individual prediction and observations showed that the effect of changes in endogenous E2 concentrations might explain a considerable part of the fluctuations in the SHBG and, indirectly, LNG concentrations.

References:

[1] Dowsett M, Attree S, Virdee S, Jeffcoate S. Oestrogen-related changes in sex hormone binding globulin levels during normal and gonadotrophin-stimulated menstrual cycles. Clinical Endocrinology (1985), 23, 303-312.

III-66: *Su-jin Rhee* A population pharmacokinetic analysis of levetiracetam in patients with epilepsy

Su-jin Rhee(1), Jung-Won Shin(2), Sang Kun Lee(3), Kon Chu(3), In-Jin Jang(1)
(1)Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea; (2)Department of Neurology, CHA Bundang Medical Center, CHA University, Seongnam, Korea; (3)Department of Neurology, Laboratory of Neurotherapeutics, Comprehensive Epilepsy Center, Biomedical Research Institute Seoul National University College of Medicine and Hospital, Seoul, Korea

Objectives: Levetiracetam is commonly used as mono- or adjunctive therapy for the treatment of patient with partial and generalized epilepsy. The aims of this study were to develop a population pharmacokinetic model of levetiracetam, and to evaluate the demographic and physiologic determinants of plasma levetiracetam levels.

Methods: A population pharmacokinetic analysis was performed using 632 levetiracetam concentrations in 508 patients with epilepsy, who received multiple oral levetiracetam. The First-Order Conditional Estimation with Interaction estimation method implemented in NONMEM (version 7.2) was used, which was followed by model qualification using bootstrapping and visual predictive checks (VPCs).

Results: A one-compartment open linear model with first-order absorption and additive residual error adequately described the concentration–time profiles of levetiracetam. The typical population estimates of the absorption rate constant, apparent clearance, and volume of distribution were 2.44 h^{-1} (fixed), 3.99 L/h, and 64.98 L, respectively. The inter-individual variabilities were 18.9% for the apparent clearance and 57.9% for the volume of distribution, respectively. Bodyweight, age, sex, and creatinine clearance had a statistically significant effect on the apparent clearance of levetiracetam, while body weight only had a statistically significant effect on the volume of distribution. Concomitant intake of other anti-epileptic drugs had no significant effect on both apparent clearance and volume of distribution of levetiracetam. Model evaluation by bootstrapping and VPCs indicated that the proposed model was adequate, robust, and stable, and the parameters were estimated with a good precision.

Conclusions: The population pharmacokinetic parameters for oral levetiracetam were successfully estimated in the patients with epilepsy using sparse data. This population pharmacokinetic model can be utilized to evaluate the relationship between levetiracetam level and occurrence of adverse event or seizure.

III-67: *Sophie Rhodes* Previous BCG vaccination associated with variation in Mycobacterial-specific immune response: a modelling study

Sophie J Rhodes (1), Gwenan M Knight (2), Jeremie Guedj (3), Helen Fletcher (4), Richard G White (1)
(1) TB Modelling Group, CMMID, TB Centre, London School of Hygiene and Tropical Medicine, (2) National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance, Imperial College London, (3) INSERM, University Paris Diderot, (4) Immunology and Infection Department, London School of Hygiene and Tropical Medicine

Objectives: Mathematical modelling could give us mechanistic insight into dynamics of immune response following vaccination and the ability to quantify the differences in these responses attributed to population covariates. We use modelling techniques to investigate the immune response to vaccination with Tuberculosis (TB) vaccine, Bacillus Calmette–Guérin (BCG) as a better understanding of the variation in response is required to develop a new vaccine against TB disease. We aimed firstly to develop an immune model of the immune response dynamics after BCG vaccination in humans, and to calibrate the model to data. Secondly, we investigated whether population covariates helped reduce variability in predicted model parameters.

Methods: We use IFN-γ as a marker of BCG vaccination immunogenicity and as such, use available ELISPOT data on IFN-γ emitting $CD4^+$ T cells over time after vaccination in 55 humans. Human population covariates were: BCG vaccination status (previously BCG vaccinated (BCG:Y) or naïve (BCG:N) at enrolment), time since BCG vaccination (including "never"), gender and monocyte to lymphocyte cell count ratio. The model was a two-compartmental, ODE model describing the dynamics of $CD4^+$ effector and memory T cells incorporating a Gaussian "delay" model representing the delay in initiation of $CD4^+$ responses following vaccination. Nonlinear mixed effects modelling implemented in Monolix[1] was used to estimate population parameters. The analyses conducted were: i) calibrate model to the human data and ii) assess the impact of human population covariates on immune model parameter values. Bayesian Information Criteria (BIC) alongside graphical results were used to assess fit.

Results: Preliminary results suggest i) the immune model with a combined residual error model represented the data well. ii) the covariate BCG status was associated with a significant ($p<0.05$) difference in immune model parameter values; those in the BCG:Y group showed significant increases in parameters associated with increased baseline and peak of response. All other covariates were non-significantly associated.

Conclusions: This analysis suggests that previous BCG vaccination is associated with durable IFN-γ responses. Vaccine trials may need to stratify by BCG vaccination history. Mathematical modelling has provided mechanistic insight into the variation in immune response dynamics and how mathematical modelling could be a vital tool to accelerate vaccine development.

References:

[1] Monolix: Users Guide v. 4.3.3 (2014).

III-68: *Jakob Ribbing* Predicting reductions in chronic obstructive pulmonary disease (COPD) exacerbations from FEV1 – A model-based meta-analysis of literature data from controlled randomized clinical trials

Jakob Ribbing (1,2,3), Julia Korell (2,4), Frank Cerasoli (1,5), Peter A. Milligan (1), Steven W. Martin (1), Mats O. Karlsson (2)
(1) Pfizer LTD; (2) Uppsala University. Current employment: (3) Pharmetheus AB; (4) Model Answers Pty Ltd; (5) Medical Dynamics

Objectives: To describe the relationship between forced expiratory volume in one second (FEV_1) and annual rate of moderate-severe[1] exacerbations (ER) utilizing summary-level, literature data.

Shorter duration Phase 2 studies assess FEV_1 whereas Phase 3 chronic maintenance studies assess the registerable endpoint (prevention of COPD exacerbations).

Methods: Data was extracted from 29 randomized trials (80 treatment arms), of 43 472 patients. As predictors of ER, model-predicted trough FEV_1[2] at baseline and Week 12, as well as covariates, were investigated using NONMEM. Placebo ER was a function of covariates and interstudy variability. The ER ratio (treatment vs. placebo) was described by separate functions for FEV_1 efficacy ($\Delta\Delta FEV_1$) from direct bronchodilators (long-acting; LABD) and anti-inflammatory (AI) agents. Outcomes were derived as point estimate [95%-Confidence interval] versus placebo/reference arm.

Results: The final model predicted that placebo ER increased with a) disease severity (FEV_1%Predicted), b) fraction of (ICS experienced) patients required to wash out from ICS ($ICS_{washout}$), and c) inclusion criteria requiring a history of exacerbations.

The log(ER-ratio) (treated vs untreated), was described by separate linear-slopes for LABD and AI $\Delta\Delta FEV_1$, and in addition for $\%ICS_{washout}$; by a $\Delta\Delta FEV_{1AI}$-E_{max} model. The model predicted that for log(ER-ratio) < -0.2 (>18% ER reduction), LABDs must achieve at least a $\Delta\Delta FEV_1$ 122 mL [114mL−132mL] improvement (over placebo/reference). For a scenario with 62% $ICS_{washout}$, an AI treatment (ICS or PDE4i) must achieve at least a $\Delta\Delta FEV_1$ 45 mL [17mL−79mL] improvement, for log(ER-ratio) < -0.2.

Conclusions: The investigated AIs have modest efficacy on FEV_1, but if patients are washed out from ICS, these treatments achieve reductions in ER comparable to the new-generation LABD. The outcomes from this analysis may be applied while designing Phase 3 efficacy studies, pharmaco-economic outcomes studies[3,4], and quantifying comparative effectiveness of available treatments.

References:
[1] Mario Cazzola, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J, 2008. 31(2): p. 416-69.
[2] Julia Korell, Steven W. Martin, Mats O. Karlsson and Jakob Ribbing. A model-based longitudinal meta-analysis of FEV_1 in randomized COPD trials. Clin Pharmacol Ther, 2015 Aug 14 [Epub ahead of print].
[3] Julia F. Slejko, Richard J. Willke, Jakob Ribbing and Peter Milligan. Translating Pharmacometrics to a Pharmacoeconomic Model of COPD.
[4] Richard J. Willke, Julia F. Slejko, Jakob Ribbing and Peter Milligan. Calibration of a Health Economic Microsimulation Model to Pharmacometric Model-Based Meta-Analysis Predictions: A Chronic Obstructive Pulmonary Disease Example.

III-69: *Camille Riff* First population pharmacokinetic model of lidocaine tumescent anaesthesia in women undergoing breast cancer surgery

C. Riff (1), A. Marsot(1), A. Bourgoin(2) J. Dupouey(1), C. Martin(2), L. Alanioux(1), O. Blin(1), R. Guilhaumou(1)

(1)Service de Pharmacologie Clinique et Pharmacovigilance, AP-HM, Pharmacologie intégrée et interface clinique et industriel, Institut des Neurosciences Timone – AMU-CNRS 7289, Aix Marseille Université - Marseille (France), (2)Service d'Anesthésie Réanimation, Hôpital Nord - Marseille (France).

Objectives: In breast cancer, tumescent lidocaine anaesthesia could increase accessibility to mastectomy in elderly women with comorbidities and relieve post-operative pain. In this procedure, high-dose diluted lidocaine was administrated together with epinephrine [1]. However, few pharmacokinetics data are actually available and potential concentration dependant toxicity was never investigated. We present in this study the first pharmacokinetic model of lidocaine in tumescent anaesthesia for mastectomy with safety and post-operative pain data.

Methods: Elderly women undergoing total mastectomy were included in this prospective study. A tumescent solution containing 10 mg/kg of lidocaine 0.1% with epinephrine was infiltrated. Lidocaine serum concentrations were determined using gas chromatography in the course of 48h and were analysis by a population pharmacokinetic approach using NONMEM 7.3. Age, body weight and body mass index (BMI) were investigated as covariates. Side effects, opioid requirement and post-operative pain evaluated by EVA scale were registered.

Results: Ten women were included and patients' characteristics were as follow (mean±sd):79 ±5 years, 67.7 ±12.5 kg and a BMI of 27.5 ±5. No symptoms of local anaesthetic systemic toxicity were observed. EVA scales registered were above 2 during the 48h and no opioid treatment was required. Lidocaine maximal observed concentration (1.65 ±0.56µg/ml) occurred 6.3 ±2.9 hour after the beginning of infusion. A one-compartment model with zero-order and first-order input for infiltration and infusion respectively, best described the data. Clearance, volume of distribution and first-order absorption rate were (intersubject variability) 30.2 L/h (65.1%), 390 L (57.6%) and 0.19 h^{-1} (44.3%), respectively. No covariate significantly improves predictions although diagnostic plots shown a trend between body weight and volume of distribution.

Conclusions: We developed the first pharmacokinetic model of lidocaine administered in tumescent anaesthesia. Lidocaine pharmacokinetics was characterized by a quick absorption after subcutaneous infiltration with a wide-interindividual variability, followed by an extensive and absorption-limited distribution. Moreover, our results demonstrate that tumescent lidocaine anaesthesia is a safe and effective anaesthetic procedure in mastectomy, with an additional effect on post-operative pain. Additional studies with larger cohorts are necessary to confirm these results.

References:

[1] Klein JA., Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. J Dermatol Surg Oncol. 1990 Mar;16(3):248-63.

III-70: *Clémence Rigaux* Parasitemia clearance modeling following Ferroquine administration in P. Falciparum infected patients

Clémence Rigaux, Marion Bouillon-Pichault, Bernard Sébastien, Kimiko Koiwai, Cathy Cantalloube
Sanofi R&D, Paris, France

Objectives: Ferroquine (FQ) is an anti-malarial drug currently being developed in combination with OZ439. Population pharmacokinetic models of FQ and its active metabolite SSR97213 after oral administration have been developed internally using blood concentration-time data from a pool of phase I and II studies that include healthy adult subjects, as well as adult and paediatric patients. The objective of this analysis is to develop and qualify a population pharmacokinetic-pharmacodynamic (PKPD) model for FQ and its active metabolite SSR97213 to describe parasitemia clearance using data from a Phase II study (DRI10382) in *P. falciparum* infected patients.

Methods: Data from the FQ-alone arm of a Phase IIb study were used to develop a non-linear mixed effect model using Monolix 4.3.3. PK and parasitemia data came from 79 symptomatic adult and paediatric (4-74 years) patients receiving 4 mg/Kg/day of FQ over 3 days. FQ and SSR97213 PK were described by the already available PK model. Parasite counts after rescue therapy or re-infection were discarded from the development database.

Results: Parasitemia was described by a simple first-order model. Periodic oscillations were applied to both first-order growth and degradation phase and a FQ effect on degradation phase was applied using an Emax function. A parasitemia threshold was used as an estimate of parasitemia below which recrudescence will not occur. In order to get unbiased diagnostic plots, a time-to-event model for rescue-therapy intake was also developed, where rescue-therapy intake depends on parasitemia levels and time. Diagnostics plots like VPC show that the model correctly predicts parasitemia for early times.

Conclusions: This model is a first step for developing a PKPD parasitemia model for the FQ-OZ439 combination. This FQ model, combined with an OZ439 model and data coming from the FQ/OZ439 combination, could be used to simulate clinical efficacy endpoints for different dosing regimens of FQ-OZ439 combinations in adults and children.

III-71: *Christelle Rodrigues* Population pharmacokinetics of oxcarbazepine and its 10-monohydroxy derivative in epileptic children

Christelle Rodrigues, Catherine Chiron, Elisabeth Rey, Gérard Pons, Vincent Jullien
INSERM, U1129

Objectives: Oxcarbazepine is a recent antiepileptic drug (AED) used in focal seizures in both children and adults. Its activity is mostly due to its major metabolite, MHD. The aim of this study was to develop the first parent-metabolite population pharmacokinetic model in order to evaluate the consistency between the recommended pediatric doses and the target trough concentration of MHD (Cmin) for therapeutic drug monitoring.

Methods: The data used were provided by a published non compartmental study of oxcarbazepine and its 10-monohydroxy derivative [1]. They included 31 epileptic children (2-12y) who were randomized to receive a single oral dose of 5 or 15 mg/kg. Blood samples were collected at times 0, 1, 2, 4, 6, 8, 12, 24, 36 and 48h. A parent-metabolite pharmacokinetic model was developed with NONMEM 7.3. Data below the limit of quantification were handled using M3 method [2]. The probability to obtain Cmin between 3-35 mg/L [3] were determined by Monte Carlo simulations with doses of 10, 20, 25, 30 and 40 mg/kg/day.

Results: A parent-metabolite model with two compartments for oxcarbazepine, one compartment for MHD and first-pass metabolism was the best to describe the pharmacokinetics of the two compounds. The parameter estimates were, for oxcarbazepine, Ka = 2.51 h^{-1}, CL = 28 (43.2%) L/h, Vc = 97.2 (43.8%) L, Q = 43.6 (79.9%) L/h and Vp = 476 L, and for MHD, a fixed fraction of the oral dose directly converted to MHD by first-pass effect of 10%, Ka = 2.47 h^{-1}, CL = 1.39 (22.1%) L/h and Vc = 8.4 (26.1%) L. Clearance of MHD was related to body weight via an allometric model. For younger children, doses of 20 to 30 mg/kg/day allowed more than 90% of Cmin to be within the target range and, for older children, doses of 10 to 25 mg/kg/day were necessary to obtain the same results. Inducing AEDs increased MHD clearance when age was greater than 6y. At 10 mg/kg/day, the probabilities to be within the range were 71.5% and 87.8% for children with and without inducing associated AEDs, respectively. At 40 mg/kg/day, these probabilities were 98.7% and 82.3%, respectively.

Conclusions: The first parent-metabolite population PK model of oxcarbazepine was successfully developed and evidenced that the doses currently used are appropriate to obtain trough concentrations of MHD within the recommended target range.

References:

[1] E. Rey, C. Bulteau, J. Motte, A. Tran, Y. Sturm, J. D'Souza, S. Markabi, G. Pons, and O. Dulac. Oxcarbazepine Pharmacokinetics and Tolerability in Children With Inadequately Controlled Epilepsy. *J. Clin. Pharmacol.*(2004) 44: 1290–1300
[2] J. E. Ahn, M. O. Karlsson, A. Dunne, and T. M. Ludden. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J. Pharmacokinet. Pharmacodyn.*(2008) 35: 401–421
[3] P. N. Patsalos, D. J. Berry, B. F. D. Bourgeois, J. C. Cloyd, T. A. Glauser, S. I. Johannessen, I. E. Leppik, T. Tomson, and E. Perucca. Antiepileptic drugs — best practice guidelines for therapeutic drug monitoring?: A position paper by the subcommission on therapeutic drug monitoring , ILAE Commission on Therapeutic Strategies. *Epi* (2008) 49(7): 1239–1276

III-72: *Stefan Roepcke* Model-based analysis of monkey PK and PD data of a therapeutic cell depleting human monoclonal antibody – Preparing for clinical trials

Stefan Roepcke, Glennda Smithson, Josh Yuan, Nele Plock, Gezim Lahu, Lin Zhao
Takeda Pharmaceuticals International

Objectives: We are studying a fully human, cell-depleting monoclonal antibody, which targets a pleiotropic transmembrane protein that is expressed on various white blood cells and up-regulated on activated lymphocytes. The antibody also binds the target and specifically depletes lymphocytes in cynomolgus monkeys and was therefore studied in several toxicology and pharmacology studies in this species. The objective of this work was to build PK-PD models based on the pooled PK and PD (changes in blood cell counts) data with the intention to gain mechanistic insights and to allow predictions of PK and PD effects in healthy human volunteers.

Methods and Results: We pooled PK and T, B, and NK cell count data (based on flow cytometric analyses) of 8 studies in healthy cynomolgus monkeys (dose range 0.03 – 100 mg/kg) and developed population PK and PK-PD models for each of the cell types. Similar to other therapeutic antibodies, the PK follows a linear 2-CMT model with a component for target-mediated drug disposition that describes non-linear elimination observed at concentrations below 0.5 µg/mL [1]. In 13-weeks toxicology studies anti-drug antibody (ADA) levels were found to increase in the majority of animals but to affect PK only above a certain threshold titer. Complete NK cell depletion was achieved with an IV dose of 0.3 mg/kg. This was adequately described with a simple turnover model (EC50=34.8 µg/mL on depletion rate). Intermediate effects on T cell counts were described with a direct response (EC50=9.43 µg/mL) and on B cell counts with a model with 4 transit compartments (EC50=19.3 µg/mL on depletion rate). Our analyses substantiate the observation that each of the measured lymphocyte subsets is cleared by the antibody at different rates and required different time spans to replete the blood compartment. In addition, we identified noticeable effects of frequent blood draws on the drop of lymphocyte counts in monkeys. The PK and PK-PD models were used to simulate PK and cell depletion profiles in monkeys and in humans after applying a straight-forward scaling approach for monoclonal antibodies. These simulations yielded predictions of exposures and effects for the ongoing First in Human clinical trial.

Conclusion: The model-based analysis of monkey PK and PD data of our cell depleting antibody provides opportunities to deepen the quantitative understanding of the pharmacology of the drug and to simulate scenarios in preparation of clinical trials.

References:
[1] Leonid Gibiansky, Ekaterina Gibiansky, Tarundeep Kakkar. Approximations of the target-mediated drug disposition model and identifiability of model parameters. Journal of Pharmacokinetics and Pharmacodynamics, 2008, Volume 35, Number 5, Page 573

III-73: *Amit Roy* Evaluating effectiveness of case-matching for exposure-response analysis

Jayson D. Wilbur (1), Manish Gupta (2) Chaitali Passey (2), and Amit Roy (2)
(1) Metrum Research Group, Tariffville CT, (2) Bristol-Myers Squibb, Lawrenceville NJ

Objectives: Accurate characterization of exposure-response (E-R) relationships can be challenging in the presence of confounding factors that affect both pharmacokinetic (PK) properties as well as response. In such situations, virtual randomization using case-matching of treatment arm subjects has been proposed to select control arm subjects for inclusion in the E-R analysis [1]. We present two approaches to evaluate the effectiveness of the virtual randomization by case-matching with respect to PK properties (that are not observable in control arm subjects).

Methods: The proposed case-matching evaluation methods are illustrated for a 2-arm clinical trial of drug (treatment) vs placebo (control), in which treatment arm subjects with exposures in the lowest quartile are matched to control arm subjects by propensity score matching. The effectiveness of the matching with respect to drug clearance (CL) is assessed by: (1) Holding out half the subjects in the treatment arm and attempting to match within the treatment arm and (2) Reverse matching the identified control subjects back to the treatment arm; and comparing exposure to what would be expected. . The validity of these methods were assessed for several simulated scenarios with varying sample sizes (N=100,200,500), covariates (p=5,10,20), and correlation among covariates and exposure (r=0.0,…,0.99).

Results: The effectiveness of case-matching improved with increasing correlation among exposure and matched covariates, and with sample size; and both evaluation methods were useful for assessing the effectiveness of the case-matching. Specifically, the percentage of held-out or reverse-matched treated subjects with exposure in the lowest quartile was predictive of the percentage of matched controls expected to have exposure in the lowest quartile. Likewise, the standardized difference in mean exposure between subjects in the lowest quartile and the held-out subjects was predictive of the standardized difference in mean exposure expected with matched controls.

Conclusions: It is recommended that effectiveness of case-matching be evaluated prior to performing exposure-response analysis on non-randomized subjects, to ensure that the matching results in balanced distributions of observed and unobserved factors that may affect both exposure and response.

References:
[1] Yang, J. et al., Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making. JCP, 53: 160–166 (2013).

III-74: *Yue Ruan* Bayesian hierarchical model of glucose-insulin regulation over 12-week home use of closed-loop insulin delivery

Y. Ruan (1,2) Malgorzata E. Wilinska (1,2) Hood Thabit (2) R. Hovorka (1,2)
(1) Department of Paediatrics, University of Cambridge, Cambridge, United Kingdom, (2) Metabolic Research Laboratories, University of Cambridge, Cambridge, United Kingdom

Objectives: Parameters of physiological models of glucose-insulin regulation in type 1 diabetes have been estimated using data collected over a relatively short period of time and lack the description of day-to-day variability. We developed a new hierarchical model to relate subcutaneous insulin delivery and carbohydrate intake to continuous glucose monitoring over 12 weeks.

Methods: Sensor glucose data (sampled every 10 min), insulin aspart delivery and meal intake were analysed from 32 adults with type 1 diabetes (male/female 4/2, age 40.8±2.6 years, BMI 25.3±3.6 kg/m^2, HbA1C 8.2±1.0 %) who underwent a 12-week home study of closed-loop insulin delivery [1]. A compartment model comprised five linear differential equations with a closed-form solution. Model parameters were estimated using the Markov chain Monte Carlo approach within a hierarchical Bayesian model framework.

Results: Physiologically plausible a posteriori distributions of model parameters including insulin sensitivity, time-to-peak insulin action, time-to-peak gut absorption, and carbohydrate bioavailability, and good model fit were observed. Day-to-day variability of model parameters was estimated in the range 38 to 79% for insulin sensitivity and 35 to 48% time-to-peak insulin action.

Conclusions: A linear Bayesian hierarchical approach is feasible to model 12-week glucose-insulin relationship using conventionally measured data.

References:

[1] Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, Acerini CL, Dellweg S, Benesch C, Heinemann L, Mader JK, Holzer M, Kojzar H, Exall J, Yong J, Pichierri J, Barnard KD, Kollman C, Cheng P, Hindmarsh PC, Campbell FM, Arnolds S, Pieber TR, Evans ML, Dunger DB, Hovorka R, Consortium AP, Consortium APh: Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129-2140

III-75: *Muhammad Waqas Sadiq* Acute tolerance and rebound modelling with competitive interaction of mineralcorticoid driven urinary sodium excretion effects in the rat

Muhammad Waqas Sadiq (1), Christine Ahlström (1), Ulrika Johansson (2), Krister Bamberg (2), Lena Williams-Olsson (2), Rasmus Jansson-Löfmark (1)
(1) CVMD iMed DMPK, AstraZeneca R&D, 431 83, Mölndal, Sweden, (2) CVMD iMed Bioscience, AstraZeneca R&D, 431 83, Mölndal, Sweden

Objectives: Mineralcorticoid receptor (MR) antagonism prevents the endogenous agonist aldosterone to retain sodium to be excreted in urine. The objective of this study was to build a quantitative understanding of this system after single doses to rats.

Methods: Various doses of aldosterone (MR agonist) and eplerenone (MR antagonist) were administered to rats in 12 different dosing combinations (n=75 rats). Animals were placed in metabolic chambers and urine was collected at serial time points for sodium excretion analysis (cumulative sodium excretion). In a separate group of animals the plasma concentrations of aldosterone and eplerenone were measured to quantify pharmacokinetic parameters. A population PK/PD model containing a pool-precursor model with competitive interaction was used to estimate the system parameters including rate and extent of tolerance, and the potencies of aldosterone and eplerenone.

Results: MR provocations displayed acute tolerance mechanisms that can be adequately described with the proposed population PK/PD model. The rate of tolerance (half-life) was estimated to approximately 4 hours. Eplerenone (MR antagonist) was estimated to be approximately 100-fold less potent than aldosterone (MR agonist). In the modelling process it was also evident that without appropriate study design, the potencies for the agonist and antagonist can easily correlate.

Conclusions: The competitive interaction mechanism for the mineralcorticoid receptor and the acute tolerance and rebound are key components that need to be considered when forward/back translating the potency of MR antagonists between species. These findings also highlights that when similar experimental setup to those described above are used in a clinical setting, the tolerance, feedback and competitive interaction need to be considered.

III-76: *Richard Pugh* Data Science & Big Data: An Opportunity or a threat for Pharmacometrics?

Richard Pugh
Mango Solutions

Objectives: In recent years, the analytic world has become awash with buzz phrases such as "data science" and "big data", with organisations across a variety of sectors investing heavily to become more "data-driven". There are close parallels between the worlds of data science and pharmacometrics with opportunities and potential threats to both from this shift to proactive analytics.

Methods: Experience gained within the wider “data science” community provides a unique perspective on the rapid growth and demand for proactive analytics and how this can relate to the aims, constraints and behaviours found in the world of Pharmacometrics. The increasing “data science” demands in terms of core skills, techniques and approaches are evaluated to determine their alignment with the pharmacometrics world.

Results: Pharmacometricians are, by definition, early "data science" adopters in respect of the skills being sought by world-leading organisations. The identification of gaps in the pharmacometricians' typical skillsets can help identify opportunities for further training. Analysis of how the analytics function is structured within other organisations provides a key to how analytics could be further exploited in the world of PKPD. At first glance, the world of “big data” would seem to have nothing to offering to the world of pharmacometrics, since it is aimed at harnessing data sizes that are not present in life sciences. However, if we ignore the “big data” label, there are opportunities that can be harnessed (such as data streaming and distributed computing). Not only are there opportunities, but many of the required skills to exploit these opportunities already exist in the pharmacometricians’ day-to-day lives (for example, an understanding of cluster computing).

Conclusions: Pharmacometricians are certainly "data scientists” based on their skillsets and remit. However, there are further opportunities in this evolving “data science” field that could be harnessed to great effect.

References:

[1] Justin J. Wilkins, E. Niclas Jonsson. Reproducible Research. PAGE Meeting, Glasgow (2013)
[2] S Locke (2015, November 20). Launching the Data Science Radar [blog]. Retrieved from http://www.mango-solutions.com/wp/2015/11/launching-the-data-science-radar/
[3] R Pugh (2015, June 25). The Single Most Important Skill for a Data Scientist [blog]. Retrieved from http://www.mango-solutions.com/wp/2015/06/the-single-most-important-skill-for-a-data-scientist/

IV-01: *Nikita Sakhanenko* New information-theory-based methods in the analysis of childhood development data

Nikita Sakhanenko, Jamiul Jahid and David Galas
PNDRI

Background. The burden of childhood diarrhea and malnutrition remains high in South Asia due to inadequate household sanitation, lack of access to improved water and poor hygiene practices. An understanding of how impaired growth is causally related to pathogen-specific diarrhea and what household factors determine this relationship can aid development of interventions that more effectively reduce these co-morbidities.

Methods. Our method is model-free and identifies multivariable dependencies among variables. The dependency measures are significantly nonzero only if the subset of variables has an essential, collective dependency. Calculating dependency values for variable sets of large degree allows us to identify the dependent subsets, but can result in combinatorial explosion. We have taken advantage of the properties of the measure to avoid the combinatorial explosion by following the "shadows" that the multi-variable dependency casts onto smaller subsets.

Results. We analyzed a large, high-dimension data set on the development of Singapore children. This study collected a diverse range of information about children to capture a full view of child development. We considered three categories of phenotypes, anthropometric, neurological, and asthma/eczema, and their dependence on genetic variation. We identified a small set of strong two- and three-variable collective dependencies among phenotypes and SNPs. These dependencies formed interconnected networks of variables, and allowed us to look for biological relationships in these dependencies and form new hypotheses about the causal relationships.

Discussion. The application of our method to the Singapore data (GUSTO) shows promising initial results – we have identified dependencies in very large and heterogeneous data, and generate hypotheses. We will now add other types of data to the analysis, and integrate them into a single network.

Several lessons: Preprocessing data is extremely important. Missing data and noise strongly affect our ability to detect dependencies, and binning variable quantities is also key. Binning ranges from segmenting real values to complex groupings of time series or categorical values. Our method returns a set of candidate multi-variable dependencies, which is input to functional analysis. The SNP-phenotype dependencies and their networks suggest a number of involved biological pathways.

Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative

IV-03: *Celine Sarr* Capacities of NPDE, VPC and pvcVPC at detecting model misspecification: a simulation study of a PK model showed no apparent difference

Anaïs Glatard (1), Thomas Dumortier (1), Jean-Louis Steimer (1), Céline Sarr (1)
1. Pharmacometrics, Novartis, Basel, Switzerland

Objectives: Simulation-based methods such as Normalised-Prediction Distribution Errors (NPDE)[1], Visual Predictive Check (VPC) and prediction- and variability-corrected VPC (pvcVPC)[2] are commonly used to evaluate pharmacometric models. There is a lack of clarity about the respective capacities of these methods at detecting model misspecification. For instance, pvcVPC intends to remove the covariate-induced heterogeneity in prediction distribution by prediction and variability correction[2]. But, by design, this correction may possibly not remove all the heterogeneity in case of model non-linearity; if this is so, pvcVPC would display wide simulated percentiles 95%CI and show weaknesses at rejecting a wrong model. The capacity of these different methods at detecting a misspecified model was investigated in the context of high non-linearity and covariate heterogeneity.

Methods: A 2-compartment and a 1-compartment PK models (true and wrong models, respectively) were defined in 2 situations: 1. the heterogeneity was introduced by an allometric relationship of the weight on the peripheral volume of distribution for the true model and on the central volume of distribution for the wrong model; 2. unrealistic covariate values were used to test the prediction and variability correction in extreme cases of heterogeneity and the covariate was introduced as a linear relationship on the absorption constant. In both situations, 1000 simulations of prediction distributions per covariate level were performed before and after correction, with both models using R. A dataset including 5 subjects per covariate level with the true model was simulated and used to estimate the true and the wrong model and to generate NPDE, VPC and pvcVPC (using NONMEM and PsN).

Results: The results for the situation 1 and 2 were similar. After correction and across covariate levels, the distributions of the predictions obtained by the true (or the wrong model) have same mean and same standard error. But the distributions still had some degrees of heterogeneity in shape. The wrong model was rejected by the 3 methods after visual inspection of the respective plots.

Conclusions: Although the prediction and variability correction did not completely remove the heterogeneity of the predictions distribution across covariate levels, the remaining heterogeneity did not prevent the pvcVPC method to detect model misspecification. Similar conclusions would be reached with NPDE and pvcVPC for the model building decision.

References:
[1] Comets E, Brendel K, Mentre F. Computing normalized prediction distribution errors to evaluate nonlinear mixed-effects models: the npde add-on package for R. Computer Methods and Programs in Biomedecine, 2008, 90:154-166.
[2] Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-Corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS Journal, 2011, 13(2):143-151

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

IV-04: *Nina Scherer* Pharmacokinetic and Pharmacodynamic Modeling of Alirocumab and Evolocumab, two fully human monoclonal antibodies targeting PCSK9

Nina Scherer (1), Christiane Dings (1), Michael Böhm (2), Ulrich Laufs (2) and Thorsten Lehr (1)
(1) Clinical Pharmacy, Saarland University, Saarbruecken, Germany, (2) Clinic of Internal Medicine III, Cardiology, Angiology and Intensive Care Medicine, Saarland University, Homburg/Saar, Germany

Objectives: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a soluble protein that enhances low density lipoprotein cholesterol (LDLc) receptor degradation and thus lowers LDLc uptake by liver cells [1]. Alirocumab and Evolocumab are two human monoclonal antibodies inhibiting PCSK9. Aim of this analysis was to develop a pharmacokinetic and pharmacodynamic (PK/PD) model for Alirocumab and Evolocumab.

Methods: Data was digitized from different published studies describing Alirocumab and Evolocumab PK as well as the resulting LDLc levels in humans for various doses (single and multiple doses between 75mg and 300mg for Alirocumab [2–6]; single dose and multiple doses between 7mg and 420mg for Evolocumab [7–9]). The dataset consisted of 112 and 100 mean plasma concentrations for Alirocumab and Evolocumab, respectively and 86 and 209 mean LDLc measurements as changes from baseline with different mean LDLc baseline levels for each mean curve. The PK/PD model was developed stepwise: first, a PK model for each compound was developed and second, the PK models were linked to the PD model to describe the change in LDLc from baseline. Model parameters were estimated using NONMEM (version 7.3).

Results: A two-compartment model with a first-order absorption and a saturable elimination described the PK of both antibodies best. LDLc levels were described by a turn over model with a zero-order synthesis rate and first-order degradation rate. At time point zero the degradation rate were determined by the baseline LDLc level. Antibody concentrations in the central compartment increased the LDLc degradation rate and decreased the LDLc synthesis rate using an Emax function. Regarding the lack of individual data, no covariates affecting the PK/PD of PCSK9 antibodies were investigated.

Conclusion: A PK/PD model describing the link between Alirocumab and Evolocumab pharmacokinetics and LDLc levels was presented for the first time. The model may serve as an excellent tool to simulate different dosing regimens and the impact of different LDLc baseline levels on the response.

References:
[1] W. R. H. Brendan M. Everett, Robert J. Smith, “Reducing LDL with PCSK9 Inhibitors - The Clinical Benefit of Lipid Drugs,” N. Engl. J. Med., 2015.
[2] M. Farnier, “PCSK9: From discovery to therapeutic applications,” Arch. Cardiovasc. Dis., vol. 107, no. 1, pp. 58–66, 2014.
[3] M. James P. Smith, MD, “Food and Drug Administration Center for Drug Evaluation and Research. Briefing Document: Praluent (alirocumab) injection,” The Endocrinologic and Metabolic Drugs Advisory Committee Meeting, 2015. [Online]. Available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM449865.pdf.
[4] A. Kumar, D. D. Jones, M. A. Hanna, B. Soediono, and A. C. Bartocci, “Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol,” J. Chem. Inf. Model., vol. 53, no. 3, pp. 556–581, 2009.
[5] C. Lunven, T. Paehler, F. Poitiers, A. Brunet, J. Rey, C. Hanotin, and W. J. Sasiela, “A randomized study of the relative pharmacokinetics, pharmacodynamics, and safety of alirocumab, a fully human monoclonal antibody to PCSK9, after single subcutaneous administration at three different injection sites in healthy

subjects," Cardiovasc. Ther., vol. 32, no. 6, pp. 297–301, 2014.
[6] J. E. Sang M. Chung, "Center for Drug Evaluation and Clinical Pharmacology and Biopharmaceutics Review," 2014. [Online]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000ClinPharmR.pdf.
[7] C. S. Dias, A. J. Shaywitz, S. M. Wasserm an, B. P. Smith, B. Gao, D. S. Stolman, C. P. Crispino, K. V. Smirnakis, M. G. Emery, A. Colbert, J. P. Gibbs, M. W. Retter, B. P. Cooke, S. T. Uy, M. Matson, and E. A. Stein, "Effects of AMG 145 on low-density lipoprotein cholesterol levels: Results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins," J. Am. Coll. Cardiol., vol. 60, no. 19, pp. 1888–1898, 2012.
[8] J. V. Suryanarayana Sista, Justin Earp, Nitin Mehrotra, "Center for Drug Evaluation and Clinical Pharmacology and Biopharmaceutics Review," 2014. [Online]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125522Orig1s000ClinPharmR.pdf.
[9] Amgen Inc, "Background Information for Endocrinologic and Metabolic Drugs Advisory Commitee," 2015. [Online]. Available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM450072.pdf.

IV-05: *Emilie Schindler* PK-PD modeling of VEGF, sVEGFR-1, sVEGFR-2, sVEGFR-3 and tumor size as predictors of overall survival in axitinib-treated metastatic renal cell carcinoma (mRCC) patients

Emilie Schindler (1), Michael A. Amantea (2), Lena E. Friberg (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) Pfizer Global Research and Development

Objectives: To investigate the predictive ability of drug exposure, circulating biomarkers (the vascular endothelial growth factor VEGF and its soluble receptors sVEGFR-1, sVEGFR-2, sVEGFR-3) and tumor sum of longest diameters (SLD) on overall survival (OS) in patients with metastatic renal cell carcinoma.

Methods: OS data were available from a phase II study including 64 Japanese mRCC patients treated with oral axitinib at a starting dose of 5 mg b.i.d continuously and followed up for a median time of 65 weeks [1]. Individual parameter estimates from previously-developed models were used to predict daily area under the curve (AUC) and the time-course of biomarkers and SLD [2]. Patients were assumed to stay on treatment until time of death or censoring. Parametric time-to-event models were fitted to the OS and to the censoring data. Baseline hazard distribution was investigated as constant, Weibull, Gompertz, log-normal and log-logistic. Baseline Eastern Cooperative Oncology Group (ECOG) status, daily AUC, the model-predicted time course and absolute/relative change from baseline over time in the biomarkers and in SLD, and the relative SLD change from baseline at week 6 were evaluated as predictors of OS, one by one and in combination.

Results: A log-logistic model with a shape factor greater than 1 best described the baseline hazard for OS which first rises, then decreases monotonically. A competing log-logistic function described the hazard of being censored. In the univariate analysis SLD time-course (dOFV=-20.9), baseline SLD (dOFV=-13.8) and sVEGFR-2 time-course (dOFV=-7.9) were statistically significant predictors of OS (p=0.01). When SLD time-course was included in the model none of the other predictors further improved the fit. Larger SLD were associated with a lower survival probability.

Conclusions: The SLD time-course best predicted OS in axitinib–treated mRCC patients. These results differ from the ones in sunitinib-treated gastro-intestinal stromal tumor patients, where sVEGFR-3 was a better predictor of OS than SLD [3]. In a next step, safety biomarkers including diastolic blood pressure will be modelled and investigated as predictors of OS

Acknowledgements: This work was supported by the DDMoRe project (www.ddmore.eu) and the Swedish Cancer Society.**References:**
[1] Tomita et al. Eur J Cancer (2011); 47: 2592-2602.
[2] Schindler et al. PAGE (2013); Abstr 2859.
[3] Hansson et al. CPT:PSP (2013); 2: e84.

IV-06: *Johannes Schropp* Development and implementation of drug-drug interaction mechanisms with target-mediated drug disposition

Johannes Schropp (1), William J. Jusko (2) and Gilbert Koch (3)
(1) Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany (2) Department of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo NY, USA (3) Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital of Basel (UKBB), Basel, Switzerland

Objectives: We extend competitive, uncompetitive and non-competitive drug-drug interaction (DDI) mechanisms with target-mediated drug disposition (TMDD). We investigate quasi-equilibrium (QE) [1] and quasi-steady state (QSS) approximations [2] for DDI TMDD models and present the implementation in standard PKPD software.

Methods: The QE- or QSS approximation of DDI TMDD systems contains a coupled non-linear equation system for the complexes. Such a model form is a so-called differential-algebraic equation (DAE). In contrast to the single drug case, explicit solving of these equation systems with respect to the free drug concentrations is challenging or even impossible [3]. Hence, two solutions are possible for implementation: (i) implementation of the DAE form, or (ii) development of an equivalent reformulation as ordinary differential equation without any equation system.

Results: Implementation of the DAE and the equivalent ODE form is presented in NONMEM (ADVAN9) and R. Fundamental differences of the QE or QSS approximation of the DDI TMDD system compared to the single drug case exist. For example, special considerations are necessary for intravenous bolus administrations. For complex DDI TMDD systems, the QSS approximation is no longer appropriate to reduce all binding rates by their dissociation constant.

Conclusions: Implementation of QE or QSS approximations of DDI TMDD systems is no longer straightforward compared to the single drug case. We developed an ODE formulation which can be simply implemented in any PKPD software. Further fundamental differences compared to the single drug case are revealed and discussed.

References:
[1] Mager DE, Krzyzanski W (2005) Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharm Res 22(10):1589-96
[2] Gibiansky L, Gibiansky E, Kakkar T, Ma P (2009) Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn 35(5):573-91
[3] Yan X, Chen Y, Krzyzanski W (2012) Methods to solving rapid binding target-mediated drug disposition model for two drugs competing for the same receptor. J Pharmacokinet Pharmacodyn 39(5):543-60

IV-07: *Partho Sen* Identification of foods with optimal nutritional value through data mining.

Partho Sen,Adil Mardinogulu,Jens Nielsen*,GEM Team# -representing the Healthy Birth,Growth and Development knowledge integration (HBGDki) community.
Department of Biology and Biological Engineering. Chalmers University of Technology. Kemivägen 10. SE-412 96. Göteborg. Sweden.

*Contact :- Jens Nielsen, email:- nielsenj@chalmers.se

Background: Exclusive breastfeeding for 6 months has been shown to be the optimal way of feeding for the healthy growth and development of infants. It is also an integral part of the reproductive process with important implications for the health of mothers. Review of evidence has shown that, on a population basis, exclusive breastfeeding for 6 months is the optimal way of feeding infants. While breastfeeding is a natural act, it is also a learned behaviour, and several factors drive early ceasation of breastfeeding. Poor breastfeeding and complementary feeding practices, coupled with high rates of infectious diseases, are the principal proximate causes of malnutrition during the first two years of life. Complementary feeding is defined as the process starting when breast milk alone is no longer sufficient to meet the nutritional requirements of infants, and therefore other foods and liquids are needed, along with breast milk.

Objectives: The objective of the study was to identify foods that have similar dietary contents as human milk.

Methods: Firstly, we listed the traditional or most consumed foods from various continents and compared them with human milk based on their dietary contents. A correlation-based distance measure (CBDM) metric was formulated for foods/diets classification. Secondly, in order to extend the search for similar food, we have deployed a computational framework coupled with a database of 8672 food/diets and 519 compounds with concentration profiles for food screening. Thirdly, Genome-scale models (GEMs) were used to understand the influence of similar food on *in silico* growth of tissues; liver (hepatocytes), fat (adipocytes) and skeletal muscle (myocytes).

Results: Lack of similarity was marked between human milk and traditional foods in any of the food groups. Mineral and vitamin content in African diets were marked low. Correlation-based screening identified foods such as goat milk (Spearman's correlation ($\rho = 0.936$), quark with fruit ($\rho = 0.927$), cheese ($\rho = [0.915-0.925]$) and yoghurt ($\rho = 0.902$) similar to human milk. Quark with fruit has been recommended for growing infants.

Conclusion: Current feeding guidelines are based more on tradition and speculation than scientific evidence, or are far more prescriptive than is necessary regarding issues such as the order of foods introduced and the amounts of specific foods to be given. We have identified at least 19 foods that have similar dietary content as human milk. These foods could aid in formulation of infant formula or given as a complementary foods together with breast milk. Moreover, the study suggests that the dietary regime of Africa should be revised and foods with high nutritional values should be included.

#Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative.

IV-08: *Ben Small* Changes in liver volume – a population-based approach to meta-analysis of paediatric, adult and geriatric populations

Ben G Small*, Bernd Wendt*, Masoud Jamei, Trevor N Johnson * Joint first author contribution
Simcyp (a Certara Company), Sheffield, UK

Objectives: Liver volume is a critical parameter for both donor / recipient graft size and as a scaling factor for drug clearance in physiologically-based pharmacokinetic modelling; therefore having an accurate and precise estimation of this parameter is essential. The objective of this study was to extend an existing meta-analysis for the estimation of liver volume to other ethnic groups and paediatric and geriatric specific populations using non-linear mixed effect modelling techniques.

Methods: Extraction of medical subject heading terms from 64 publications assessing the measurement and / or prediction of liver volume allowed construction of a search string that enabled the objective retrieval of records from the PubMed® database. Parsing of retrieved records to ensure relevance to liver volume assessment was achieved by filtering records against exclusion criteria. Missing body size parameters were simulated within the Simcyp Simulator v14.1 for an age appropriate population. Non-linear mixed effect modelling was undertaken in Phoenix 1.3 (Pharsight) utilising backward deletion and forward inclusion of covariates from fully parameterised models. Existing liver volume models based on body surface area (1, 2) and bodyweight & height (3) were implemented for the purposes of comparison.

Results: Extension of a structural model predicated on a BSA equation and incorporating the Japanese race and age as co-variates and exponents on LV0 (θBaseline) and body surface area (θBSA) respectively delivered a comparatively low OFV. Bootstrapping of the original dataset revealed that the confidence intervals (2.5 – 97.5 %) for the fitted (theta) parameter estimates were bounded by the bootstrapped estimates of the same.

Conclusions: These results demonstrate that extension and re-parameterisation of the existing Johnson model provides an adequate descriptor of body surface area-dependent changes in liver volume.

References:

1. Johnson TN et al. Liver transplantation. 2005;11:1481-93.
2. Urata K et al. Hepatology1995;21:1317-21.
3. Yu HC et al. Liver Transplantation. 2004;10:779-83.

IV-09: *Kevin Smart* Modeling tumor size time course in platinum resistant/refractory ovarian cancer patients treated with vanucizumab

Kevin Smart (PhD), Christophe Boetsch (PharmD) , Francois Mercier (PhD), Valerie Cosson (PhD), Vincent Buchheit (MSc), Oliver Krieter (MD), Alex Phipps (PhD), Benjamin Ribba (PhD)
Roche Innovation Centre Welwyn, UK

Objectives: Longitudinal modelling of tumor lesion diameter data is a useful technique allowing extraction of key metrics of tumor shrinkage, visualization of tumor burden over time and comparison of effect between different treatments. In this work, this technique was applied to platinum (Pt)-resistant/ refractory Ovarian Cancer (PROC) patients treated with Vanucizumab, a novel bi-specific IgG-like antibody directed against both VEGF-A and ANG2, two key factors in tumor angiogenesis.

Methods: Longitudinal data from forty PROC patients treated with vanucizumab (30 mg/kg IV Q2W) were analyzed using non-linear mixed effects modelling techniques. Patients underwent tumor assessment by CT scan at screening, (approximately 8-weeks prior to Cycle 1 Day 1) and then every 8 weeks (wks) while on study. Overall, the data set contained 143 observations (mean 3.6, range 2-6 per patient), and pts received on average 9 cycles of treatment. Data were analyzed using the population model described by Claret et al (2009), using the SAEM algorithm of NonMEM 7.2. The analysis provided quantitative estimation of metrics of efficacy, such as maximum shrinkage and time to tumor regrowth, together with critical kinetic parameters, such as the natural growth rate of the tumor, and resistance to treatment. Resultant model parameters were used to simulate data from 1000 random patients, whose maximum shrinkage and time to regrowth were summarized, allowing comparison with other therapies.

Results: The maximum tumor shrinkage from baseline was calculated to be 49% (95% CI: 47-52%), with a time to re-growth of 5.5 months (95% CI: 5.2-5.7 months). The population estimate of the resistance parameter was 0.02 day^{-1}. The unperturbed tumor growth rate was estimated to be 0.001 day^{-1}.

Conclusions: The Claret model adequately described the data in PROC patients. The estimated values of the tumor size metrics provided refined information on the clinical activity of Vanucizumab, in addition to those supplied by RECIST criteria.

References:
[1] Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics. Laurent Claret et al, 2013. JCO 27: 4103-4108.

IV-10: *Mike Smith* Model Description Language (MDL) - a standard for model communication and interoperability

MK Smith (1), S Moodie (2), R Bizzotto (3), E Blaudez (4), E Borella (5), L Carrara (5), P Chan (1), M Chenel (6), E Comets (7), R Gieschke (8), K Harling (9), L Harnisch (1), N Hartung (10), A Hooker (9), MO Karlsson (9), R Kaye (11), C Kloft (10), N Kok

(1) Pfizer; (2) Eight Pillars Ltd; (3) Consiglio Nazionale delle Ricerche; (4) Lixoft; (5) Universita di Pavia; (6) Servier; (7) INSERM; (8) Roche; (9) Uppsala Universitet; (10) Freie Univeristät Berlin; (11) Mango Solutions; (12) Novo-Nordisk; (13) Cyprotex; (14) EMBL-EBI; (15) Merck.

Objectives: The DDMoRe Model Description Language (MDL)[1] and Pharmacometrics Markup Language (PharmML)[2] standards have been developed to convey information about models and tasks. MDL provides a means for modellers to describe and understand pharmacometric models irrespective of the tool used for analysis, while PharmML provides the basis for interoperability between software tools. The aim of this work is to show that MDL can be used to define models that are interoperable across modelling software tools and that are also easy to understand and share.

Methods: In developing MDL we have looked at features in established languages and adopted features that will facilitate interoperability, while retaining the flexibility to describe complex models. Having a well-defined software interchange standard (PharmML) and mapping MDL into PharmML allows us to focus on describing model features with one target in mind – PharmML. MDL conveys, in an accessible, user (analyst) friendly way, the models that can be encoded in PharmML. Converter tools then interpret the PharmML rather than the MDL for each software target. Testing this conversion and comparing output downstream allows us to check the translation.

Results: At the time of writing, MDL has been used to encode 10 Use Cases shared as part of the DDMoRe software installation describing common population pharmacokinetic model features and simple efficacy models with non-continuous outcomes. These models have been shown to be interoperable across commonly used NLME software: NONMEM, Monolix and simulx. The Design and Prior objects in MDL facilitate use with optimal design software such as PFIM and Bayesian software such as WinBUGS. Over 40 models have been encoded in MDL, published and shared via the DDMoRe Model Repository. These models cover disease areas such as oncology, CNS, infectious diseases. In excess of 60 delegates have been trained in MDL via the DDMoRe disease area training courses.

Conclusions: The interoperability of the Use Cases proves the desired outcome that a single model expressed in MDL can be used within a Pharmacometric workflow for a variety of tasks regardless of what target software is available to the user. Encoding models for the DDMoRe repository using MDL ensures that these models are readily understandable and shareable. Training pharmacometricians in MDL, a lingua franca, allows models and modelling concepts to be consistently defined, independent of software tools.

References:

[1] N Holford, MK Smith. MDL - The DDMoRe Modelling Description Language. PAGE 22 (2013) Abstr 2712 [www.page-meeting.org/?abstract=2712]

[2] MJ Swat et al. Pharmacometrics Markup Language (PharmML): Opening New Perspectives for Model Exchange in Drug Development. CPT: Pharmacometrics & Systems Pharmacology (2015) **4**; 316-319. http://dx.doi.org/10.1002/psp4.57

IV-11: *Victor Sokolov* A mechanistic PKPD model relating early asthmatic response to anti-leukotriene drug PK and biomarker levels in allergen challenge studies

Victor Sokolov (1), Tatiana Yakovleva (1), Kirill Zhudenkov (1), Anne-Kristina Mercier (2), Ulf Eriksson (2)
(1) M&S Decisions, Moscow, Russia (2) Quantitative Clinical Pharmacology, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Gothenburg, Sweden

Objectives: Inhibition of leukotriene (LT) production in asthmatic patients attenuates the drop in Forced Expiratory Volume in 1 second (FEV1) after allergen provocation [1]. Measurement of LTE4 (uLTE4) levels in urine is an efficacy biomarker used in early phase clinical development, while FEV1 is an endpoint of choice in later phases. FEV1 is highly variable and dependent upon multiple factors, thus the prediction of FEV1 response based on early clinical biomarker data is a challenge. Our aim was to describe the relationship between LT-inhibitor pharmacokinetics (PK), pre-challenge suppression of blood LTB4 and uLTE4 levels, and the degree of early FEV1 reduction in the context of an allergen challenge study in asthma.

Methods: Published data from clinical Phase I and II studies of a 5-Lipoxigenase-activating-protein inhibitor (GSK2190915) and a 5-Lipoxigenase inhibitor (MK-0591) were used to build the model [2-4]. Only early asthmatic response (within 2 hours after allergen challenge) was incorporated into the model.

Modeling was performed in the IQM Tools (replacing the SBTOOLBOX2 by IntiQuan - http://www.intiquan.com/). The model was based on a 2-compartment module for PK, an “Imax” transit compartment to describe the biomarker, and an indirect response function to describe the allergen challenge and the FEV1 endpoint estimation.

Results: The model reproduced uLTE4 suppression by 10-450 mg of GSK2190915 [5] and 50-500 mg of MK-0591 [6] and evidenced a quantitative link between pre-challenge uLTE4 levels and FEV1 within the first 2 hours following allergen challenge. The basic shape of the early FEV1 response was dependent upon the type of challenge and followed the same exponential form across the studies analyzed [2-4], while trough FEV1 levels were linearly dependent upon LT suppression. Predictions of FEV1 levels were in full agreement with the data reported for the 250 mg MK-0591 study (13% maximal drop in FEV1 comparing to baseline) [1] and for the 10-100 mg GSK2190915 studies (0.8-0.5 L maximal drop in FEV1 comparing to baseline) [3, 4].

Conclusions: We developed a PKPD model describing the relationship between LT-inhibitor PK, pre-allergen-challenge uLTE4 levels and early post-allergen-challenge FEV1. Such a model may be applied towards the prediction of FEV1 response in Phase II allergen challenge studies, based on Phase I compound PK and uLTE4 suppression data.

References:

[1] Pol Merkur Lekarski. 1998 Dec;5(30):317-20
[2] J Allergy Clin Immunol. 1995 Jan;95(1 Pt 1):42-51
[3] Clin Exp Allergy. 2013 Feb;43(2):177-86
[4] Int J Gen Med. 2013 Dec 9;6:897-903
[5] Br J Clin Pharmacol. 2013 Mar;75(3):779-90
[6] Br J Clin Pharmacol. 1995 Jul;40(1):59-66

IV-12: *Byungjeong Song* Application of different methodologies to explain the pharmacokinetic variabilities in pregnant women: Case study of Sulindac usage

Byungjeong Song, Hyunmoon Back, Younghoon You, Eben Jung, Nayoung Han, Hwi-yeol Yun, Kwang-il Kwon
College of pharmacy, Chungnam National University, Daejeon, Korea

Objectives: Physiological changes during pregnancy are well known and these have various effects on drug pharmacokinetics (PK). The objective of this study was to compare methodologies which could explain pharmacokinetic variabilities of sulindac in pregnant women.

Method: Blood samples from 69 patients with preterm labor whose gestational age was between 17 and 37 weeks were collected 1.5 hr, 4 hr, 10 hr after oral administration of 200 mg sulindac. Three methods were applicated to explain pharmacokinetic variability in preterm labor patients, (1) dividing gestational age into three trimesters, (2) insertion of covariate related to pregnancy status such as gestational age to PK parameters, (3) applicate gestational age functions. Pharmacokinetics of sulindac and variability was evaluated using the nonlinear-mixed-effect modeling program (NONMEM® 7.3.0). Goodness of fit plots and visual predictive checks were conducted to confirm concordance with observed data.

Results: Population pharmacokinetic parameters were estimated based on 196 plasma samples. Data were adequately described by a one-compartment model. Vd/F and CL/F of sulindac was estimated 47.6 L, 6.09 L/hr, respectively. The third method which applicate gestational age functions described the observed variability well in PK data from preterm labor patients.

Conclusion: Population pharmacokinetic models were developed which can adequately describe the plasma concentrations of sulindac in patients with preterm labor. The gestational age function was a good tools to predict pharmacokinetics in pregnant women. We plan to expland this model to include an active and an inactive metabolites of sulindac. This methodology appears to be promising, therefore its application in other drugs used in pregnancy should be further explored.

References:
[1] Charles O. Odongo, Keteesa R. Bisaso, Mugammad Nitale et al., Trimester-specific population pharmacokinetics and other correlates of variability in Sulphadoxine-Pyrimethamine disposition among Uganda pregnant women. *Drugs R D* 15:351-362
[2] Berg AK, Mandrekar SJ, Ziegler KL, et al., Population pharmacokinetic model for cancer chemoprevention with sulindac in healthy subjects. *J Clin Pharmacol* 53(4):403-12

IV-13: *Amaia Soraluce* Population pharmacokinetics of linezolid in critically ill patients and treatment probability of target attainment

A. Soraluce, H. Barrasa, E. Asín, E. Irazusta, A. Martín-López, S. Castaño Ávila, G. Balziskueta, F. Fonseca, J. Maynar, J.A. Sánchez-Izquierdo, F. Muñoyerro, A. Rodríguez-Oviedo, A. Rodríguez-Gascón, A. Isla
University of The Basque Country

Objectives: The main goal of this study was to build a population PK model for the antibiotic linezolid (LZD) in Intensive Care Unit (ICU) patients, treated or not with Continuous Renal Replacement Therapies (CRRT). Another aim was to apply PK/PD analysis with Monte Carlo simulation to predict safety and efficacy profiles.

Materials and methods: 45 adult ICU patients were included in the study, 26 of whom underwent CRRT. All patients received a 30 min infusion of linezolid (600 mg) every 12 hours. Blood and ultrafiltrate samples (when necessary) were collected during dosage interval (DI) and their LZD concentration was determined by a previously validated HPLC technique.

A population PK model was developed using NONMEM 7.2. Once base model was selected, covariates related to demographic and physiopathological aspects were considered in order to explain inter-individual variability (IIV). Stepwise covariate model building (SCM) was used. Parameter precision was evaluated by performing a 2000 dataset bootstrap.

In order to predict the probability of target attainment (PTA) for different DI (12 and 8 h), studies of 5000 subjects with several CL_{CR} values were simulated using parameters obtained from the PK model. The target was attained when AUC_{24}/MIC was greater than 100 [1]. Moreover, LZD´s security profile was evaluated, taking into consideration the percentage of simulated subjects that would reach toxic plasma concentrations (AUC_{24} >400 mg*h/L or Cmin >10 mg/L) [2]. Simulations were performed using mlxR package of R program.

Results: LZD plasma concentrations were best described by a 2 compartment model. IIV was included using an exponential model in CL (56.8%) and V_1 (78.1%). CL was set as the sum of a non-renal (Θ =2.8 L/h) and a renal (Θ =3.68 L/h) component, which was influenced by CL_{CR}. In those patients with CRRT, extracorporeal clearance was included in CL as a fixed value for each individual.

PK/PD analysis showed high PTA (> 90%) for MIC values equal or lower than 0.25 mg/L. When simulations were run for a dosage of 600 mg every 8 h, no improvement was achieved, while higher probabilities of drug overexposure were obtained [3].

Conclusions: The PK/PD analysis confirmed that LZD is not able to cover infections by pathogens for which the MIC values are higher than 0.25 mg/L, which is far away from the established clinical breakpoint (2 mg/L) [4], even when increasing the dosage to 600 mg every 8 h.

References:
[1] Pea F, Viale P, Cojutti P et al. Therapeutic drugmonitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012; 67:2034–42.
[2] Cattaneoa D, Orlandob G, Cozzia V, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with Gram-positive infections. Int J Antimicrob Agents. 2013;

41:586-589.
[3] Gerson SL, Kaplan SL, Bruss JB, et.al. Hematologic Effects of Linezolid: Summary of Clinical Experience. Antimicrob Agents Chemother. 2002 Aug; 46(8): 2723–2726. doi: 10.1128/AAC.46.8.2723-2726.2002.
[4] Asin E, Isla A, Canut A, Rodriguez-Gascón A et al. Comparison of antimicrobial pharmacokinetic/pharmacodynamic breakpoints with EUCAST and CLSI clinical breakpoints for Gram-positive bacteria. Int J Antimicrob Agents. 2012; 40:313-322.

IV-14: *Konstantina Soulele* A population pharmacokinetic study of salmeterol in asthmatic patients using two dry powder inhalers

Konstantina Soulele, Panos Macheras, Vangelis Karalis
Laboratory of Biopharmaceutics-Pharmacokinetics, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

Objectives: To apply population pharmacokinetic modeling in order to describe the concentration-time (C-t) profile of salmeterol in asthmatic patients after administration of two dry powder inhalers (DPI).

Methods: Salmeterol plasma C-t data were obtained from a single dose 2x4 bioequivalence study comparing two dry powder inhalers in 48 asthmatic male and female subjects under fasting conditions, without co-administration of activated charcoal. Non-linear mixed-effect modeling was applied to the obtained C-t dataset. Since, no charcoal was administered, apart from the pulmonary, gastrointestinal (GI) absorption could also occur. A pharmacokinetic model capable of describing the parallel lung and GI absorption was developed. Many residual error models were tested, whereas age, gender, body weight, and height were explored as potential covariates. The entire computational work was implemented in Monolix v.4.3.3.

Results: A two-compartment disposition model with first order absorption from the GI and very rapid absorption from lungs (like IV bolus) was found to describe successfully the C-t profiles of all patients. Elimination was considered to take place in the central compartment following first order kinetics. The model was parameterized in terms of the GI absorption rate constant (Ka), apparent volume of distribution in the central (Vc/F) and the peripheral (Vp/F) compartment, as well as apparent clearance (CL/F) and inter-compartmental clearance (Q/F). The relative fraction of dose absorbed (Rpo) through the GI was set as a parameter estimated by the optimization process. The application of a proportional error model led to the optimum performance. The following pharmacokinetic parameters were estimated: Ka = 0.325 h^{-1}, Rpo = 0.85, Vc/F = 218 L, Vp/F = 2970 L, Q/F = 339 L/h, and CL/F = 408 L/h. Gender was found a significant covariate on salmeterol clearance. Men were found to exhibit higher clearance than women, a finding that is in agreement with that observed in healthy subjects [1]. Body weight was also found a significant covariate on the volume of distribution of the central compartment. As body weight increases, the value of this parameter also rise. No difference in the performances of the two DPIs was observed.

Conclusions: A population pharmacokinetic model, with parallel GI and lung absorption was found to describe successfully the C-t profile of salmeterol in asthmatic patients. Women exerted less capability to eliminate salmeterol than men.

References:
[1] Soulele K, Macheras P, Silvestro L, Rizea Savu S, Karalis V. Population pharmacokinetics of fluticasone propionate/salmeterol using two different dry powder inhalers. Eur J Pharm Sci (2015) 80: 33-42.

IV-15: *Spyros Stamatelos* High-Resolution Image-based Computational Modeling of Breast Tumor Microvasculature

Spyros K. Stamatelos1, 2, Arvind P. Pathak2, Aleksander S. Popel2
1Roche Innovation Center, New York, NY, USA, 2Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Objectives: The goal of the project is to develop a computationally intensive model to characterize a whole human tumor xenograft comprised of a population of thousands of vessels. Specifically, the platform cast as blood flow model which processes the output of a graph-based algorithm we developed to delineate blood flow transport in the heterogeneous tumor angiogenic network. This computational model can have wide implications as a simulation tool to design efficacious chemotherapeutic and antiangiogenic strategies [1].

Methods: The xenograft data were obtained from inoculation of human breast cancer cells in the mammary fat pad of mice. The high-resolution images were processed in a graph-based algorithm we developed to reconstruct and repair the morphological discrepancies of the initial image. These imaging data were the input to a blood flow model accounting for pressure drop and blood rheology in all the functional segments of the tumor vasculature. An optimization algorithm was used to ensure mass balance in all the inputs and outputs of the vascular system allowing exchange of blood with an extravascular compartment. Morphological and hemodynamic metrics were calculated for the entire tumor vasculature and various regions of interest. Model development was completed using MATLAB and Java Eclipse programs.

Results: The image-based computational model was successful in processing the whole population of imaging vascular segment data allowing the generation of detailed blood perfusion maps for the whole network and regions of interest. The metrics of both structural (diameter, length) and functional (velocity, hematocrit) characteristics of individual segments were calculated and compared.

Conclusions: Tumor vasculature is extremely heterogeneous and therefore there is a dire need to develop computational tools to characterize it both structurally and functionally [2]. This analysis can facilitate the evaluation of tumor in various stages of progression and provide an assessment tool for targeted therapies.

References:
[1] Stamatelos, S. K., Kim, E., Pathak, A. P. & Popel, A. S. A bioimage informatics based reconstruction of breast tumor microvasculature with computational blood flow predictions. *Microvascular research* **91**, 8-21, doi:10.1016/j.mvr.2013.12.003 (2014).
[2] Kim, E. *et al.* Multiscale imaging and computational modeling of blood flow in the tumor vasculature. *Annals of biomedical engineering* **40**, 2425-2441, doi:10.1007/s10439-012-0585-5 (2012).

IV-16: *Oleg Stepanov* A quantitative systems pharmacology model to explore combination efficacy of immuno-oncology compounds: Effects of CXCR2 and PD-1 inhibitions

Oleg Stepanov, Veronika Voronova, Yuri Kosinsky, Kirill Peskov, Eric Masson, Gabriel Helmlinger
M&S Decisions

Objectives: Targeting of the tumor microenvironment and of immune cell-dependent mechanisms is a promising emerging approach for the treatment of different cancers [1]. As monotherapies in a preclinical setting, neither anti-CXCR2 induced decrease in myeloid-derived suppressive cells (MDSC) influx into tumor tissue, nor T-cell checkpoint inhibition via an anti- PD1 antibody significantly affect tumor growth; however, their combination results in impressive tumor growth inhibition [2]. The main aim of this study was to provide mechanistic hypotheses relative to the synergistic effects of combined anti-CXCR2/anti-PD1 treatment, using quantitative systems pharmacology (QSP) modeling. A related goal was to identify system parameters driving inter-animal variability in the observed tumor dynamics responses.

Methods: A QSP model was built upon a set of ordinary differential equations. Tumor dynamics was described by a logistic equation and was directly driven by the time-dependent number of activated cytotoxic lymphocytes (CTL). In the model, tumor growth itself promoted MDSC migration into tumor tissue, a mechanism which may directly inhibit CTL proliferation. Activated CTLs would also negatively affect their own activation via a PD1-dependent negative feedback mechanism. The dynamics of CXCR2 and PD1 antibodies were described using, respectively, one-compartment and two-compartment PK models. The effects of CXCR2 blockade on MDSC migration and of PD1 blockade on free PD1 levels were described using Imax equations. Qualification of the QSP model was based on various data published in the literature [2].

Results: The proposed model adequately described tumor dynamics and CTL levels in control experiments, in CXCR2 and PD1 monotherapies, and in their combination. A local sensitivity analysis of the model demonstrated that inter-animal variability in response to treatment depended mainly on parameters describing the dynamics of active CTLs and their infiltration into tumor tissue. It was also shown that, even for modest changes in these specific parameter values, the output response (tumor dynamics) could be switched from unaffected tumor growth to full tumor growth inhibition or regression. Such quantitative insights may form the basis for the elucidation of patient response vs. no response, as observed in recent immuno-oncology clinical trials [REF].

Conclusions: A preclinical QSP model of the immuno-oncology cycle, which includes mechanisms of action for CXCR2 and PD-1 inhibitions, was developed, based on experimental data published in the literature. It was shown that simultaneous targeting of these two immuno-suppressive pathways would lead to sufficient immune cell activation as well as inhibition of immuno-suppressive MDSCs in the microenvironment, with a net result of tumor growth inhibition or regression. A set of model parameters, critical for a positive treatment outcome and possibly explaining the broad heterogeneity observed in inter-individual responses, was also identified via a model-based sensitivity analysis.

References:
[1] Chen DS and Mellman I. Oncology Meets Immunology:The Cancer-Immunity. Immunity, 2013, 39, 1-10.
[2] Highfill SL, Cui Y, Giles AJ. Disruption of CXCR2-mediated MDSC tumor trafficking enhancesefficacy. Sci Transl Med. 2014 May 21;6(237):237ra67

IV-17: *M. Elena Suarez Gonzalez* How delayed or missed doses influence efficacy of amoxicillin in outpatients with community-acquired pneumonia: A pharmacokinetic/pharmacodynamic simulation analysis

Suarez E(1) , Carral N(1), Estrade O(1), Jauregizar N(1), Lukas JC(1,2).
(1) Department of Pharmacology, School of Medicine, University of the Basque Country, Spain (2)Current affiliation: Drug Modeling & Consulting, Dynakin SL, Derio, Spain

Objective: The purpose of this study was to quantify the impact on efficacy of non adherence to treatment by amoxicillin in outpatients with community-acquired pneumonia.

Methods: A dose dependent (absorption) amoxicillin population PK model parameters [extracted from Sjövall published data (1)] was used to simulate the pharmacokinetic profiles of amoxicillin after an empirical dosing protocol (1000 mg/8h) on pneumonia produced by *S Pneumoniae*. Virtual outpatients (weight 70 kg) were divided in subgroups according to age (young: 18-25 years; adults: 25-65 years; and elderly: 65-80 years) and interindividual variability in creatinine clearance calculated according the Cockcroft-Gault formula, based on demographic characteristics and serum creatinine (Crs) (0.7-1.3 mg/dl). Treatment control and non-compliance scenarios were applied in simulation across age and Crs levels, for a missed or delayed dose (1, 2, 3, 4, 6, 8h delays), and the impact on drug exposure calculated for patient proportions (Monte Carlo simulations). The probability of target attainment ($fT>MIC_{90}$ less than 50% as PK/PD predictor of antimicrobial efficacy), was calculated in each scenario, with a 90% clinical efficacy threshold (2).

Results: The medium PK parameters estimated from the public domain model extraction were for absorption rate constant=0.63 , apparent volume of distribution = 23.3 L, and different range of apparent clearance were established depending on Crs= 13.2-24.6 L/hr (young adults), 10.8-20.1 L/hr (adults) and 7.2-13.4 L/hr (elderly), similar to those reported elsewhere. Monte Carlo simulations of amoxicillin plasma concentrations in 10k virtual patients were done using the model above. In patients with Crs= 0.7 mg/dL (elderly) the probability of target attainment was less than 90% for a delay in drug intake > 2 hours, but in young and adults no delay can be allowed. In patients with Crs between 0.8 and 0.9 mg/dL, efficacy impacting delay times are >1h (young); >2h (adults); >6h (elderly). In patients with Crs of 0.9-1.3 mg/dL the corresponding prohibitive delays are 2-3h, 4-6h and 8h in young, adult and elderly, respectively.

Conclusion: In non-adherent dosing scenarios for virtual outpatients of different age and physiological interindividual variability on creatinine clearance, amoxicillin dose 1000 mg/8h was not always able to achieve the PK/PD index guaranteeing clinical efficacy in community-acquired pneumonia, especially in young patients with a Crs inferior to 0.9 mg/dL.

References:
[1] Sjövall J, Alvan G, Westerlund D. Dose-dependent absorption of amoxycillin and bacampicillin. Clin Pharmacol Ther 1985; 38:241-250
[2] Asín-Prieto E, Rodriguez-Gascon A, Isla A. Applications of the pharmacokinetic/pharmacodynamics (PK/PD) analysis of antimicrobial agents. J Infect Chemother 2015; 21:319-29

IV-18: *Siddharth Sukumaran* A quantitative systems pharmacology model for evaluating potential drugs for treatment of asthma

Kapil Gadkar, Siddharth Sukumaran, Tracy Staton, Manoj Rodrigo, Cynthia Stokes, Heleen Scheerens, Saroja Ramanujan
Genentech, USA

Background: Asthma is a chronic inflammatory disease of the airways involving numerous underlying immunological and stromal pathways. Various treatments in development target activities or proteins in these pathways, and show differential impact on clinical outcomes and pathway biomarkers. Although specific molecular pathways are being characterized more thoroughly, the understanding of the linkage between the underlying mechanisms with the functional clinical outcomes is still very limited. Given this limited mechanistic understanding and to expedite clinical research, a human experimental model of rhinovirus (RV) infection challenge is being developed to support a proof-of-activity study to evaluate drug candidates as a means to prioritize and expedite clinical research.

Methods: We have developed a mechanism-based systems model representing different cellular and soluble contributors to asthma, including (1) innate immune, adaptive immune, and airway resident cells (2) soluble proteins such as IL5, IL13, IL4, and IgE and (3) clinical markers and endpoints such as FeNO and FEV1. The model has been developed utilizing preclinical in vitro and in vivo data, and clinical data for multiple drugs including anti-IgE, anti-IL5, anti-IL13, and anti-IL-4Rα. The model was then utilized for making predictions for novel mono and combination therapies to support clinical decision making. To further expedite the clinical development of drug candidates the model includes the RV infection challenge representation and predictions were made for responses of mild asthmatics on the RV challenge to treatment.

Results: The model was calibrated and verified to successfully describe the clinical measurements for different patient severities and for a range of interventions. The model is used for making predictions for existing mono therapies (including anti-IL13, anti-IL-4Rα) and novel combination therapies and identifying patient sub-populations that respond favorably to the different interventions. The model is also utilized to design the proof-of-activity RV clinical study.

Conclusions: The model is useful to elucidate biological pathways underlying observed effects of the different interventions and allows us to explore and predict the impact of additional interventional strategies for which little to no clinical data is available.

IV-19: *Robin Svensson* Population pharmacokinetic modeling to assess the non-linear increase in exposure following increasing doses of rifampicin

Robin Svensson (1), Rob Aarnoutse (2), Andreas Diacon (3), Rodney Dawson (4) Stephen Gillespie (5), Martin Boeree (6) and Ulrika Simonsson (1)

(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands, (3) DST/NRF Centre of Excellence for Biomedical Tuberculosis Research and MRC Centre for TB Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Tygerberg, South Africa and TASK Applied Sciences, Cape Town, South Africa, (4) Department of Respiratory Medicine, University of Cape Town, Cape Town, South Africa and The Lung Institute, Cape Town, South Africa (5) The Medical School, University of St. Andrews, St. Andrews Fife, United Kingdom, (6) Department of Lung Diseases, Radboud University Medical Center, Nijmegen, the Netherlands and University Centre for Chronic Diseases Dekkerswald, Groesbeek, the Netherlands

Objectives: There is evidence suggesting that the current dose of rifampicin for treatment of tuberculosis (TB) is suboptimal. In a recent multiple dose rising trial, rifampicin was well tolerated at 40 mg/kg daily where unexpectedly high exposures were observed at the higher doses [1]. Our objective was to quantify the non-linear exposure using non-linear mixed effects modeling in order to assist in the optimization of the rifampicin dose.

Methods: Data consisted of plasma pharmacokinetic (PK) samples from 83 pulmonary TB patients given daily rifampicin of 10 (reference arm, n=8), 20, 25, 30, 35 or 40 (n=15/arm) mg/kg for 14 days, as monotherapy for 7 days and combined with isoniazid, pyrazinamide and ethambutol for the following 7 days [1]. Blood samples were drawn at days 7 and 14 with rich sampling between 0 and 24 hours. Data were analysed in NONMEM 7.3 [2] with log-transformation both sides. Model evaluation was done by comparison of objective function value (OFV) and diagnostic plots. The M3 method was used to handle observations below the limit of quantification. Auto-induction was accounted for by an earlier developed enzyme turn-over model [3]. Allometric scaling of clearance (CL) and volume (V) was investigated using different body size descriptors [4]. Different absorption models were evaluated. Non-linearity in exposure was evaluated in CL and bioavailability (F). Concentration-dependency was evaluated in CL using linear and Michaelis-Menten relationships. Dose-dependency was investigated in F.

Results: A one-compartment model with a transit absorption compartment model with a Michaelis-Menten relationship on CL described exposure in all dose groups and at the two dosing occasions (days 7 and 14). Model predicted fold increase in $AUC_{0\text{-}24h}$ compared to a standard 10 mg dose in a typical patient (54 kg) at day 14 was 2.6, 4.0, 5.6, and 8.0 for 20, 30, 40 and 50 mg/kg of rifampicin.

Conclusions: A rifampicin population PK model was developed accounting for exposure-dependent auto-induction, allometric scaling and non-linear decrease in CL at higher doses. The model allows for clinical trial simulations in order to optimize the dose of rifampicin.

References:

[1] Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, Phillips PPJ, Gillespie SH, McHugh TD, Hoelscher M, Heinrich N, Rehal S, van Soolingen D, van Ingen J, Magis-Escurra C, Bruger D, Plemper van Balen G & Aarnoutse RE. A dose ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med (2015) 191(9): 1058-1065.

[2] Beal S, Sheiner LB, Boeckmann A & Bauer RJ. NONMEM Users Guides. 1989-2013. Icon Development Solutions, Ellicott City, Maryland, USA.
[3] Smythe W, Khandelwal A, Merle C, Rustomjee R, Gninafon M, Bocar Lo M, Sow OB, Olliaro PL, Lienhardt C, Horton J, Smith P, McIlleron H & Simonsson USH. A semimechanistic pharmacokinetic-enzyme turnover model for rifampin autoinduction in adult tuberculosis patients. Antimicrob Agents Chemother (2012) 56(4): 2091–98.
[4] Anderson BJ & Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol (2008) 48: 303–32.

Acknowledgments: The research was funded by the Swedish Research Council and the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement n°115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

IV-20: *Eva Sverrisdóttir* Pharmacokinetic Metamodel of Morphine and Morphine-6-Glucuronide in Neonates and Adults

Eva Sverrisdóttir (1), David John Richard Foster (2), Anne Estrup Olesen (1,3), Trine Meldgaard Lund (1), Asbjørn Mohr Drewes (3,4), Lona Louring Christrup (1), Mads Kreilgaard (1) & Richard Neil Upton (2)
(1) Department of Drug Design and Pharmacology, Faculty of Health Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark, (2) Australian Centre for Pharmacometrics, School of Pharmaceutical and Medical Sciences, City East Campus, North Terrace, University of South Australia, Adelaide SA 5000, Australia, (3) Mech-Sense, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Mølleparkvej 4, DK-9000 Aalborg, Denmark, (4) Department of Clinical Medicine, Aalborg University, Sdr. Skovvej 11, DK-9000 Aalborg, Denmark,

Objectives: Morphine is the gold standard opioid to treat moderate to severe pain. Morphine-6-glucuronide (M6G) is an active metabolite and contributes to the effect of morphine [1]. The pharmacokinetics (PK) of morphine and M6G are associated with large inter-individual variability, which makes optimal dose selection challenging, especially in populations such as neonates and patients with renal impairment [2]. The aims of this study were to develop a combined morphine and M6G PK metamodel in neonates and adults, identify covariates that explain some of the large variability, and describe the formation of M6G after administration of morphine through different routes.

Methods: Morphine and M6G data from 22 studies in diverse populations were fitted to PK models using NONMEM 7.3 [3]. Morphine was administered through the intravenous, oral, intramuscular, rectal, and subcutaneous route. M6G was administered intravenously in four studies, and metabolite M6G concentrations were available in 15 studies. Study populations included healthy volunteers, preterm neonates, and patients with renal impairment. Model development of the combined PK metamodel consisted of three stages. First, morphine concentration-time data was fitted to PK models and optimised regarding random effects and covariates. Second, M6G data was included in the model and the M6G PK model was developed, with the morphine model fixed. Lastly, the formation of M6G after administration of morphine was estimated and covariates were tested for the M6G model.

Results: Morphine and M6G PK were described with two-compartment PK models. Absorption of morphine after oral, rectal, and subcutaneous administration was described with transit compartment absorption models. A sigmoidal maturation model defined as a function of postmenstrual age described the maturation of morphine clearance in neonates. In adults, morphine clearance was shown to decrease with age. M6G formation constituted 17% of morphine clearance. In addition, 26% of an oral or rectal dose was formed to M6G (first-pass metabolism). Creatinine clearance was included as a covariate for M6G clearance.

Conclusions: Some of the large inter-individual variability in morphine and M6G PK was explained with weight, age, creatinine clearance, and postmenstrual age. The formation of M6G was described after administration of morphine, with additional first-pass metabolism for the oral and rectal route.

Acknowledgements: Data was kindly provided by Albert Dahan, Camilla Staahl, Hanne Villesen, Pernille Ravn, Anne Brokjær, Felix Bochner, Mark Dershwitz, Richard Osborne, Magdi Hanna, Ola Dale, Thor Bjelland, Ingolf Meineke, John van den Anker, Brian Anderson

References:

[1] Binning, A.R., Przesmycki, K., Sowinski, P., Morrison, L.M., Smith, T.W., Marcus, P., Lees, J.P., Dahan, A., 2011. A randomised controlled trial on the efficacy and side-effect profile (nausea/vomiting/sedation) of morphine-6-glucuronide versus morphine for post-operative pain relief after major abdominal surgery. Eur. J. Pain 15, 402-408.
[2] Somogyi, A.A., Barratt, D.T., Coller, J.K., 2007. Pharmacogenetics of opioids. Clin. Pharmacol. Ther. 81, 429-444.
[3] Beal, S.L., Sheiner, L.B., Boeckmann, A.J., Bauer, R.J., 1989-2013. NONMEM 7.3.0 Users Guides. 7.3.0.

IV-21: *Maciej Swat* PharmML & SO - standards for encoding models and results in PMX and QSP

Maciej J Swat (1) and Nadia Terranova (2), on behalf of all DDMoRe contributors
(1) EMBL-EBI, Cambridge, UK (2) Merck Institute for Pharmacometrics, Merck Serono S.A., Switzerland.

Objectives: New formats enabling the efficient exchange and integration of pharmacometric (PMX) and quantitative system pharmacology (QSP) models across software tools have been defined and implemented as key elements of the DDMoRe interoperability platform [1]. Specifically, PharmML has been designed as the exchange medium for mathematical and statistical models [2, 3], and the Standard Output (SO) has been developed as a complementary component for storing typical output produced in a PMX workflow.

Methods: PharmML has been devised as a declarative language for mathematical and statistical models. Its development has been based on requirements provided by the DDMoRe community, popPK/PD and QSP partners, and on specific use cases from the main target tools (NONMEM, Monolix and BUGS). SO has been designed to be a tool-independent storage format providing a flexible structure for main results produced in PMX analyses. For this purpose, numerical results from target tools were collected, compared and classified in order to define and to implement a suitable structure able to account for typical output results. These two formats are subject to continued testing performed by a group of modellers and developers within DDMoRe, including academic and EFPIA partners. Standards extension to include additional features is ongoing.

Results: PharmML provides a structure for encoding continuous and discrete data models equipped with complex variability structure, covariate, structural and observation models. Definition of clinical trial design and modeling steps is possible as well. As a comprehensive self-contained format, it allows to encode models in tool agnostic manner [4]. SO is capable to capture any type of results from target tools including estimation, optimal design and clinical trial simulation tasks, thus, enabling effective data flow across tasks, and facilitating information retrieval for post-processing and reporting. These two formats facilitate (i) smooth and error-free transmission of models between tools, (ii) use of complex workflows via standardized model and output definitions, (iii) reproducibility of research, (iv) bug tracking and (v) development of new tools and methods.

Conclusions: PharmML and SO, as essential elements of the DDMoRe interoperability platform, proved to be capable to handle complex modeling scenarios, and to facilitate model exchange and results storage across various tools.

This work is on behalf of the DDMoRe project [1].

References:

[1] DDMoRe project, www.ddmore.eu
[2] Bonate, P. (2011). Pharmacokinetic-Pharmacodynamic Modeling and Simulation. 2nd ed.
[3] Lavielle, M. (2014). Mixed Effects Models for the Population Approach: Models, Tasks, Methods and Tools. Chapman & Hall/CRC Biostatistics Series.
[4] Swat et al. (2015). Pharmacometrics Markup Language (PharmML): Opening New Perspectives for Model Exchange in Drug Development. CPT Pharmacometrics Syst Pharmacol, 4(6):316-9.

IV-22: *Yakovleva Tatiana* A systems pharmacology model of SGLT2 and SGLT1 inhibition to understand mechanism and quantification of urinary glucose excretion after treatment with Dapagliflozin, Canagliflozin and Empagliflozin

Tatiana Yakovleva, Victor Sokolov, Kirill Zhudenkov
M&S decisions, Moscow, Russia

Objectives: Sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors are a class of drugs effective for type 2 diabetes treatment [1]. However, given the overwhelming contribution (>80%) of SGLT2 to renal glucose reabsorption (rGR), it has been expected that SGLT2 inhibitors, at sufficient exposures, would reduce rGR by over 80%. This expectation appeared to be contradicted by the clinical observations that only 30–50% of inhibition in glucose reabsorption was achieved with Dapagliflozin and Canagliflozin [2]. The aim of the work was to evaluate the relative contribution of SGLT2 and SGLT1 to rGR and explain the mechanism underlying this discrepancy in clinical data, using a quantitative systems pharmacology (QSP) modeling approach.

Methods: The approach for description of gliflozin distribution and lumen concentration was taken from previously published model [1]. Recent model additionally includes kidney glucose filtration, reabsorption by SGLT2/SGLT1, and urine excretion. Available data from gliflozin clinical studies [3-5] were used to estimate parameters. The drug action mechanism implied the competitive inhibition of glucose reabsorption [2], with corresponding IC50 values [6-8]. The modeling was performed in the IQM software tool (by IntiQuan, derived from the SBTOOLBOX2 software - http://www.intiquan.com/).

Results: The QSP model adequately describes the experimental data on 24-hour UGE after treatment with Dapagliflozin, Canagliflozin and Empagliflozin for healthy subjects. The maximum contribution of SGLT2 to rGR was evaluated to 87%, correlating with in vitro data (80-90%) [9]. The contribution of SGLT2 to rGR without drug administration for healthy subjects in vivo was predicted as 77%. Under the treatment with gliflozins the contribution each of the transporters changes depending on inhibitor dose and has a 35% value for the labelled dose treatment for all considered drugs. The observed UGE level is dependent on IC50 for SGLT1/2 and lumen concentration for each of the drugs.

Conclusions: A QSP model of SGLT1/2 inhibition described the relationship between processes of renal glucose reabsorption and UGE, allowed to estimate the relative contributions of SGLT2 and SGLT1 to total rGR rate, and adequately described the experimental data after treatment with Dapagliflozin, Canagliflozin and Empagliflozin. The model was used to delineate the mechanism underlying the apparent discrepancy in UGE levels, as observed for gliflozin-type compounds.

References:

[1] Demin O Jr, Yakovleva T, Kolobkov D, Demin O. Analysis of the efficacy of SGLT2 inhibitors using semi-mechanistic model. Front Pharmacol. 2014 Oct 13;5:218.
[2] Lu Y, Griffen SC, Boulton DW, Leil TA. Use of systems pharmacology modeling to elucidate the operating characteristics of SGLT1 and SGLT2 in renal glucose reabsorption in humans. Front Pharmacol. 2014 Dec 10;5:274.
[3] Yang L, Li H, Li H, Bui A, Chang M, Boulton DW. Pharmacokinetic and pharmacodynamic properties of single- and multiple-dose of dapagliflozin, a selective inhibitor of SGLT2, in healthy Chinese subjects. Clin Ther. 2013 Aug;35(8):1211-1222.
[4] Devineni D, Curtin CR, Polidori D, Rothenberg PL. Pharmacokinetics and pharmacodynamics of

canagliflozin, a sodium glucose co-transporter 2 inhibitor, in subjects with type 2 diabetes mellitus. J Clin Pharmacol. 2013 Jun;53(6):601-10.
[5] Heise T, Seman L, Macha S, Dugi K. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of empagliflozin in patients with type 2 diabetes mellitus. Diabetes Ther. 2013 Dec;4(2):331-45.
[6] Grempler R, Thomas L, Eckhardt M. Himmelsbach F. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab. 2012 Jan;14(1):83-90.
[7] Hummel CS, Lu C, Loo DD, Hirayama BA. Glucose transport by human renal Na+/D-glucose cotransporters SGLT1 and SGLT2. Am J Physiol Cell Physiol. 2011 Jan;300(1):C14-21.
[8] Australian Public Assessment Report for Canagliflozin (Invokana, Prominad). 2014 March Therapeutic Goods Administration.
[9] DeFronzo R.A., Davidson J.A., Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. DiabetesObes. Metab. 14, 5–14.

IV-23: *Paulo Teixeira* Population Pharmacokinetics Model of Valproic Acid in Overweight Adult Patients.

Teixeira P (1), Laso E (2), Otero MJ (2), García Sánchez MJ (1), Santos Buelga D (1).
(1) Department of Pharmaceutical Science, University of Salamanca, Spain. (2) Service of Pharmacy, University Hospital of Salamanca, Spain.

Objectives: The main goal of this work was to develop an updated population pharmacokinetic model to quantify the clearance (CL) of valproic acid (VLP) in overweight adult patients.

Methods: Serum concentrations of VLP were taken from patients aged 16-78 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 192 serum concentrations from 95 patients. Pharmacokinetic analysis was performed with NONMEM V7.3 (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 and body mass index (BMI). It has been performed in the absence of other comedication and other associated diseases.

Results: It has been observed that the CL is different in overweight patients. However, it has been found that the WGT as the BMI is a valid indicator in the Spanish population, taking into account the statistical values of the Statistics National Institute (Spain). The use of WGT is an advantage because it is easier to obtain in clinical practice.

The covariate with significant influence on CL_{VLP}/F in overweight patients was: WGT according to an allometric function [4]. The proposed final model for CL_{VLP}/F was as follows:

<u>WGT < 80 kg:</u>
CL_{VLP}/F (L/h) = 0.011 × (WGT)

w^2 = 0.041

<u>WGT ≥ 80 kg:</u>

CL_{VLP}/F (L/h) = 0.65 × $((WGT/70)^{0.53})$

w^2 = 0.062

s^2= 0.052 (*shrinkage*: 19 %).

The results obtained in the Bootstrap analysis show acceptable performance of the proposed model.

Conclusions: The population pharmacokinetics model developed for VLP in overweight adult patients includes WGT. We not found a strictly proportional relationship between the CL and WGT. In overweight patients, the parameter CL appears to be related to the WGT according to an allometric function. This model appears to be adequate for clinical application in TDM. However, we consider it necessary to do an

external validation in a new patient population having similar characteristics to those of the study population.

References:

[1] Dutta S, Reed RC. Distinct absorption characteristics of oral formulations of valproic acid/divalproex available in the United States. *Epilepsy Res*. 2007; 73:275-83.
[2] Patsalos PN. *Antiepileptic drug interactions. A clinical guide.* 2nd ed. Springer; London. 2013.
[3] Serrano BB, Garcia Sanchez MJ, Otero MJ, Buelga DS, Serrano J, Dominguez-Gil A. Valproate population pharmacokinetics in children. *J Clin Pharm Ther*. 1999; 24:73-80.
[4] Holford N, Anderson B. Mechanism-Based Concepts of Size and Maturity. 2008; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500009792.pdf. Accessed January/12, 2016.

IV-24: *Rob ter Heine* The influence of erythrocyte accumulation on everolimus pharmacokinetics and pharmacodynamics in cancer patients

Rob ter Heine
Radboud University Medical Center, Nijmegen

Objectives: Everolimus is a drug from the class of mTOR-inhibitors. There is increasing concern over the need for dose reductions due to severe toxicity [1]. Everolimus pharmacokinetics and pharmacodynamics are influenced by hematocrit (HT), as everolimus extensively accumulates in erythrocytes [2]. The extent to which HT affects everolimus plasma exposure and thereby mTOR inhibition is unknown. The aim of our study was to investigate the everolimus pharmacokinetics and pharmacodynamics and the influence of HT on these parameters in cancer patients.

Methods: A semi-physiological population pharmacokinetic (PK) model for everolimus that accounted for everolimus erythrocyte accumulation and incorporated a physiological model for first-pass metabolism, as described previously [3] was developed in NONMEM. By implementing a pharmacodynamic (PD) model, describing the relationship between unbound plasma concentrations and inhibition of S6K1 (a downstream mTOR effector) [4], we investigated the impact HT on the predicted PK and PD.

Results: PK curves in whole blood from 73 cancer patients were available. HT ranged from 25% to 49.7%. Oral absorption was described with 4 transit compartments and a mean absorption time (MAT) of 0.544 h (RSE 6.4%). The apparent volume of distribution of the central and peripheral compartment were respectively estimated to be 207 (RSE 5.0%)and 485 L (RSE 4.2%), with an inter-compartmental clearance of 72.1 L/h (RSE 3.2%). The intrinsic clearance was estimated to be 198 L/h (RSE 4.3%). The inter-individual variability in MAT, intrinsic clearance and volume of distribution of the central compartment were estimated to be 62.0% (RSE 23.5%), 38.9% (RSE 24.8%) and 36.1% (RSE 63.4%), respectively. A decrease in HT of 45% to 20% resulted in a reduction in whole blood exposure of approximately 50%, but everolimus plasma pharmacokinetics and mTOR inhibition were not affected. The predicted mTOR (S6K1) inhibition was at a plateau level in the approved dose of 10 mg once daily.

Conclusions: A semi-physiological population PK model accounting for erythrocyte accumulation was developed for everolimus in cancer patients. HT influenced whole blood PK, but not plasma PK or PD. Therefore, in studies investigating the relation between everolimus PK and PD, whole blood concentrations should always be corrected for HT. Since predicted mTOR inhibition was at a plateau level, dose reductions may only have a limited impact on mTOR inhibition. This encourages further prospective studies to reduce everolimus toxicity without loss of efficacy.

References:

[1] Baselga J, Campone M, Piccart M, Burris HA, 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. The New England journal of medicine. 2012;366(6):520-9.
[2] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000_ClinPharmR.pdf
[3] Gordi T, Xie R, Huong NV, Huong DX, Karlsson MO, Ashton M. A semiphysiological pharmacokinetic model for artemisinin in healthy subjects incorporating autoinduction of metabolism and saturable first-pass hepatic extraction. British journal of clinical pharmacology. 2005;59(2):189-98.
[4] Tanaka C, O'Reilly T, Kovarik JM, Shand N, Hazell K, Judson I, et al. Identifying optimal biologic doses of

everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol. 2008;26(10):1596-602.

IV-25: *Adrien Tessier* Population Pharmacokinetic modelling and Pharmacogenetic analysis through a penalised regression approach for a molecule S

Adrien Tessier (1), Karl Brendel (1), Charlotte Gesson (1), Sylvain Fouliard (1), Emmanuelle Comets (2,3) and Marylore Chenel (1)

(1) Division of Clinical Pharmacokinetics and Pharmacometrics, Institut de Recherches Internationales Servier, Suresnes, France. (2) INSERM, IAME, UMR 1137 ; Université Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France. (3) INSERM CIC 1414, Université Rennes 1, Rennes, France.

Objectives: More and more genetic data are collected in clinical trials. Based on an example, we propose an approach to integrate a large number of genetic variants in population PK models, using a penalised regression approach recently evaluated in this context [1,2].

Methods: Drug S is a compound metabolised mainly by CYP1A2 (80%). This metabolism enzyme is highly polymorphic and numerous environmental factors (tobacco, estrogens…) can modify its expression [3], in addition to genetic factors. Data came from 10 phase I studies, including 257 healthy volunteers receiving single or repeated oral administrations. Several demographic (age, gender, BMI, BSA, ethnicity) and environmental (food, tobacco or contraceptives use) variables were measured. Subjects were also genotyped for 176 Single Nucleotide Polymorphisms (SNPs) using a DNA microarray designed for ADME genes. A population PK model was built on these data.
In the covariates model building, demographic and environmental covariates were first included in the PK model, so that genetic variants were next associated with the remaining unexplained variance of clearance (CL).
Then two pharmacogenetic (PG) analyses were performed: a targeted analysis, where only associations between 3 SNPs from CYP1A2 and CL were investigated through LRT [4]; and a blinded analysis, where associations between CL and the 176 SNPs were explored using a Lasso regression [5]. All genetic covariates selected by the Lasso were included and tested in the PK model through LRT.
Estimation of the population parameters was performed using NONMEM 7.3 and FOCE-I algorithm. Lasso analysis was performed using the HyperLasso program [6].

Results: Drug S PK data were described by a two-compartment model, with a linear elimination. Two shifted first-order absorptions were used to describe a late rebound in concentrations and bioavailability parameter F was nonlinear with dose.
Effects of food, gender, age, ethnicity and contraceptives intake were included in the PK model. One third of the CL variance was explained by these covariates. None of the two PG analyses showed significant association between genetic variants and the remaining unexplained CL variance.

Conclusion: In this approach, genetic variants, which are often associated with low to moderate effects on PK, were explored taking into account other confounding covariates. This approach could allow detecting smaller genetic effects. For drug S, no polymorphism was associated with the unexplained interindividual variability.

References:
[1] Bertrand et al. Pharmacogenet Genomics. 2013
[2] Tessier et al. AAPS J. 2015
[3] Faber et al. Basic Clin Pharmacol Toxicol. 2005
[4] Lehr et al. Pharmacogenet Genomics. 2010

[5] Tibshirani. J R Stat Soc Ser B. 1994
[6] Hoggart. PLoS Genet. 2008

IV-26: *Donato Teutonico* Whole-body PBPK/PD modelling of ciprofloxacin and its anti-bacterial activity

Kuepfer, Lars (1); Niederalt, Christoph (1); Wendl, Thomas (1); Schlender, Jan-Frederik (1); Willmann, Stefan (2); Lippert, Jörg (2); Block, Michael (1); Eissing, Thomas (1); Teutonico, Donato (1)
(1) Bayer Technology Services, Leverkusen, Germany, (2) Bayer HealthCare, Wuppertal, Germany

Objectives: The objective of this study was to develop a full blown whole-body physiologically based pharmacokinetic (PBPK) model for the antibiotic ciprofloxacin to adequately describe the patient plasma concentration of this compound. The drug concentration predicted by the model was then coupled with an in vitro pharmacodynamic (PD) model to describe anti-bacterial drug effect as function of the ciprofloxacin target exposure.

Methods: A whole-body PBPK model was built with the PBPK software tool PK-Sim® (1) including both physiological information from the software database and ciprofloxacin physicochemistry. Relevant metabolisation (CYP1A2) and excretion processes (biliary, glomerular filtration rate (GFR) and tubular secretion) were explicitly included in the model and the clearance values were estimated from published plasma concentration profiles (2). To represent administration of solid dosage forms, a Weibull function was used to describe the dissolution process. An *in vitro* PD model describing *E. coli (11775)* microbial growth (3) and its antibiotic-mediated inhibition was coupled with the ciprofloxacin lung concentration predicted by the PBPK model established. Antimicrobial activity was simulated for two dosing regimens, 500 mg BID and 1000 mg OD.

Results: The PBPK model developed was able to adequately describe measured PK plasma concentration-time profiles after intravenous as well as after oral administration. Observed PK plasma profiles, AUCs and Cmax for iv and oral dosing regimens were within the 1.5-fold range for the simulations. Elimination and excretion processes described in the model are in agreement with mass balance information available for ciprofloxacin. Target site exposure in the lung was directly coupled to the antibacterial effect of ciprofloxacin. Comparison of expected kill curves with the two tested dosing regimen tested, 500 mg BID and 1000 mg OD, showed a similar outcome for *E.coli (11775)*, with a decrease in CFU/ml > 5 log units over 24 h for both administrations, in agreement with reported literature data (3).

Conclusions: In conclusion, the PBPK/PD model developed was able to describe plasma concentration of ciprofloxacin after intravenous and oral administration, as well as to reproduce several treatment scenarios of antibacterial activity following ciprofloxacin administration.

References:
[1] Eissing T. et al. A computational system biology software platform for the multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front. Physio. (2011)
[2] Davis RL, Koup JR, Williams-Warren J, Weber A, Heggen L, Stempel D, et al. Pharmacokinetics of ciprofloxacin in cystic fibrosis. Antimicrobial agents and chemotherapy. 1987;31(6):915-9
[3] Schuck EL, Dalhoff A, Stass H, Derendorf H. Pharmacokinetic/pharmacodynamic (PK/PD) evaluation of a once-daily treatment using ciprofloxacin in an extended-release dosage form. Infection. 2005;33 Suppl 2:22-8

IV-27: *Hoai-Thu Thai* Model-based drug development to support isatuximab dosing regimen selection in Phase II multiple myeloma patients

Hoai-Thu Thai (1), Li Liu (2), Dorothée Semiond (1), Claire Brillac (1), Eric Charpentier (2), Laurent Nguyen (1), Christine Veyrat-Follet (1)
(1) Drug Disposition, Sanofi, Paris, France (2) Biostatistics and Programming, Sanofi, US

Objectives: Isatuximab (ISA) is a humanized anti-CD38 monoclonal antibody with multiple modes of action for killing tumor cells through direct tumor targeting and immune cell engagement [1]. The objective of this work was to optimize the phase II dosing-regimen of ISA in multiple myeloma (MM) patients using modeling and simulation.

Methods: The proposed framework associated exposure-response analysis with disease modeling of tumor burden. The preliminary data from a phase I/II monotherapy trial [2] included: PK, serum M-protein and best overall response (BOR) in 170 patients receiving ISA from 1 to 20 mg/kg every 2 weeks or weekly. First, we developed a population PK model for ISA then the relationship between various PK parameters and BOR was investigated in an exploratory exposure-response analysis. Baseline covariates were also considered in the model to reduce their potential confounding effects. Disease progression was captured in a subset of 122 evaluable patients with the dynamics of the serum M-protein and accounted for dropout using a joint model. Simulations were then performed to evaluate different dosing regimens of interest in terms of efficacy.

Results: ISA PK was best described by a two-compartment model with parallel linear and nonlinear elimination and time-dependence on clearance while serum M-protein kinetics was adequately described by an exposure-driven tumor growth inhibition model [3]. The exposure-response relationships (logit Emax model) suggested that high Ctrough at 4 weeks lead to better efficacy. Interestingly, patients with lower linear clearance were more likely to respond. Longitudinal modeling of M-protein provided more insights in the response of patients over time. Therefore, a high loading dose of 20 mg/kg weekly over 4 weeks was chosen for maximizing the tumor response and a maintenance dose of 20 mg/kg every 2 weeks appeared sufficient to sustain efficacy. This dosing regimen presented a probability of success of 85% to reach 30% overall response rate with 100 patients and would allow 53% reduction of serum M-protein from baseline at 2 months of treatment. In addition, ISA appeared to be well tolerated at this dose level.

Conclusions: Model-based drug development has been successfully applied to support phase II ISA dosing regimen selection in MM patients. This approach increases both the robustness of decision making and the chances of success of the future Phase III program.

References:

[1] Deckert J, Wetzel MC, Bartle LM, Skaletskaya A, Goldmacher VS, Vallée F, Zhou-Liu Q, Ferrari P, Pouzieux S, Lahoute C, Dumontet C, Plesa A, Chiron M, Lejeune P, Chittenden T, Park PU, Blanc V. SAR650984, a novel humanized CD38-targeting antibody, demonstrates potent antitumor activity in models of multiple myeloma and other CD38+ hematologic malignancies. Clin Cancer Res (2014);20(17):4574-83
[2] Martin T, Richter J, Vij R, Cole C, Atanackovic D, Zonder J, Kaufman JL, Bensinger W, Dimopoulos MA, San Miguel J, Zimmerman T, Lendvai N, Hari P, Ocio EM, Gasparetto C, Kumar S, Hsu K, Charpentier E, Strickland SA, Mikhael J. A Dose finding phase II trial of isatuximab (SAR650984, anti-CD38 mAb) as a single agent in relapsed/refractory multiple myeloma. ASH (2015). Abstract 509.
[3] Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, Fagerberg J, Bruno R. Model-based

prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. J Clin Oncol 27 (2009), 25:4103-4108.

IV-28: *Anders Thorsted* Toxicokinetics of Endotoxin and its Induction of Pro-Inflammatory Cytokines Tumor Necrosis Factor a and Interleukin-6

Anders Thorsted (1), Salim Bouchene (1), Eva Tano (2), Markus Castegren (2), Miklos Lipcsey (2), Jan Sjölin (3), Mats O. Karlsson (1), Lena E. Friberg (1) and Elisabet I. Nielsen (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala Sweden, (2) Department of Medical Sciences, Uppsala University, Uppsala, Sweden, (3) Department of Surgical Sciences, Uppsala University, Sweden

Objectives: Infection with Gram-negative bacteria and the immune system's subsequent recognition of the potent membrane-bound activator, endotoxin (ETX), can lead to persistent immune activation. The purpose of the current work was to develop a model-based description of the toxicokinetics of ETX and its induction of the cytokines tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6).

Methods: Based on data from experimental studies, a non-linear mixed effects model was developed in NONMEM 7.3. The modelled data arose from two short-term (six hours) experimental studies in an anesthetized piglet model (n=46), with the aim of studying the inflammatory immune response and organ dysfunction following ETX exposure [1-2]. In the first study, *E. coli* ETX was infused intravenously for six hours (rates ranging from 0.063 to 16.0 μg/kg/h) while the second study examined differences in response following one, two or six hours of intravenous infusion (0.063 or 4.0 μg/kg/h).

Results: The time-course of ETX could be described using a one-compartment model with non-linear elimination, with inter-batch variability included on the ETX dose. Observation of contamination in early ETX measurements was handled by initializing the central compartment to an estimated parameter. At 50% of maximum saturation (observed for rates of 4.0 μg/kg/h and above) the elimination half-life was approximately 0.8 hours. For cytokines, an indirect response model with ETX stimulated production (E_{max} model), delayed through a transit chain (three compartments), was used to describe the shape of the observed profiles. To describe tolerance development in cytokine release following ETX exposure, an exponential time-dependent increase was included in EC_{50}, the parameter describing the potency of ETX to induce cytokine production. Rapid tolerance development was identified with doubling times for EC_{50} of 1.66 (TNFα) and 7.66 minutes (IL-6). In addition, a number of previously published tolerance models were tested [3], but none were found superior to the initial more empirical implementation.

Conclusions: A mathematical description was developed for the time-course of ETX following intravenous infusion, and linked to induction of the two immune response markers TNF-α and IL-6. This model-based approach is unique in its description of the three time-courses, and may later be expanded to better understand immune cell release in bacterial infections and sepsis-type pathophysiological changes.

References:
[1] Lipcsey M, Larsson A, Eriksson MB, Sjölin J. Inflammatory, coagulatory and circulatory responses to logarithmic increases in the endotoxin dose in the anaesthetized pig. J Endotoxin Res. 2006;12(2):99-112.
[2] Carlsson M, Lipcsey M, Larsson A, Tano E, Rubertsson S, Eriksson M, Sjolin J. Inflammatory and circulatory effects of the reduction of endotoxin concentration in established porcine endotoxemic shock--a model of endotoxin elimination. Crit Care Med. 2009 Mar;37(3):1031-e4.
[3] Gårdmark M, Brynne L, Hammarlund-Udenaes M, Karlsson MO. Interchangeability and predictive performance of empirical tolerance models. Clin Pharmacokinet. 1999 Feb;36(2):145-67.

Acknowledgements: The research leading to the modelling results was partly supported by the Swedish Foundation for Strategic Research (SFF).

IV-29: *Yingying Tian* Population pharmacokinetic analysis of everolimus in patients with solid tumors

Yingying Tian(1), Christian Mattonet(2), Lucia Nogova(2), Uwe Fuhr(1)
(1)Department I of Pharmacology, University Hospital of Cologne, Cologne, Germany; (2)Lung Cancer Group Cologne, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany

Background: The combination of the mTOR inhibitor everolimus and the multi-kinase inhibitor sorafenib may increase anti-tumor efficacy, therefore the drugs are intended to be given in combination. Some factors including variable oral bioavailability and drug-drug interactions lead to high inter-individual pharmacokinetic variability of everolimus. Understanding the sources of variability may support personalized cancer management.

Objective: To develop a pharmacokinetic model for everolimus able to describe its exposure profile in patients with solid tumors.

Methods: Pharmacokinetic profiles of everolimus were obtained from a phase-I clinical trial. In its initial dose finding phase, 17 patients with relapsed solid tumors were treated with escalating everolimus doses (2.5, 5, 7.5 or 10 mg daily). A fixed dose of sorafenib 400 mg bid was added from day 15. Additionally, 13 KRAS mutated non-small cell lung cancer patients were treated in an extension phase with the maximum tolerated dose 7.5 mg/day everolimus with 400 mg sorafenib bid thereafter until progression. Everolimus concentrations were measured on day 5, 14, and 29 (pre-dose, 0.5, 1, 2, 3, 4, 8, 12, 24 h relative to morning dose) and less dense sampling was taken for the follow-up. Data were analyzed using nonlinear mixed-effects modeling implemented in NONMEM V7.3.0. The impact of different covariates such as demographics and laboratory tests on the pharmacokinetic of everolimus were evaluated and quantified.

Results: A two-compartment model with linear absorption and elimination was developed. It predicted that the total clearance would increase 55% in the presence of sorafenib, which was comparable to non-compartment analysis that the AUC and Cmax of everolimus showed a 20 - 40% reduction. Among the covariate relationships tested, everolimus pharmacokinetic characteristics were not influenced by age, body weight or sex, but clearance decreased with higher blood bilirubin. By including a power covariate relationship model the unexplained inter-individual variability could be reduced by 13.4% for clearance.

Conclusion: The current model was suitable to predict the pharmacokinetics of everolimus. It allows a better description of everolimus exposure when co-administered with sorafenib in solid tumor patients. The mechanism for the lower exposure to everolimus when co-administered with sorafenib remains to be elucidated.

IV-30: *Huybrecht T'jollyn* Pharmacokinetics of galantamine in plasma and brain for different intranasal formulations: an experimental in vivo study

H. T'jollyn(1), J. Vercruysse(2), E. De Thaye(1), J.P. Remon(2), A. Vermeulen(1), J. Van Bocxlaer(1), C. Vervaet(2)

(1) Laboratory of Medical Biochemistry and Clinical Analysis, Ghent University, Belgium; (2) Laboratory of Pharmaceutical Technology, Ghent University, Belgium

Objectives:

1. Develop a population PK model to describe plasma and brain pharmacokinetics of galantamine (Gal) in rabbits after intranasal delivery.
2. Compare bioavailability and rate of absorption between different formulations with varying composition.
3. Investigate direct nasal-to-brain transport of Gal.

Methods: For 10 different single dose formulations (intravenous and intranasal), blood was sampled from the rabbit's ear vein pre-dose and at 8 time points post-dose. For the multiple dose (MD) study, one intranasal formulation was selected and administered every hour for 5 consecutive doses. Plasma concentrations for every rabbit were measured after the first dose and then alternately after consecutive doses. Brain data were collected at every trough level, and around Tmax after the 4th dose. A nonlinear mixed-effects pharmacokinetic model was developed in NONMEM 7.2.0 (Icon Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method to describe Gal disposition in plasma and brain. Distribution to the brain was assumed to take place from the central compartment, and was described using micro-constants. The volume of the brain was fixed to a wet tissue weight of 12g [1].

Results: A two-compartment model with first-order absorption and elimination best described the plasma PK of Gal. Depending on the formulation's properties, distinct plasma concentration-time profiles were obtained, mainly resulting from differences in bioavailability (range 52-100%) and nasal rate of absorption (rate constant range 0.046-1.86 min^{-1}). In addition, the absorption rate of pure Gal base was 17 times that of pure Gal HBr powder. For the investigation of the direct nasal-to-brain transport, several structural models were tested, but none was supportive of a direct nasal-to-brain process, in contrast to earlier findings in the rat [2].

Conclusions: Gal absorption after intranasal administration differed markedly between formulations and was highest and fastest after administration of pure Gal base powder, without excipients. Extended release times can be obtained by using Amioca®/Carbopol®:API (ratio 90/10). Gal transfer from plasma to brain is the rate limiting step in its brain distribution, with no indications for a direct nasal-to-brain route in rabbits.

References:

[1] MSTE data archive. MSTE Data Archive: Body and Brain Weights. [cited 05-05-2015]; Available from: http://mste.illinois.edu/malcz/DATA/BIOLOGY/Animals.html

[2] Stevens J, Ploeger BA, van der Graaf PH, Danhof M, de Lange EC. Systemic and direct nose-to-brain transport pharmacokinetic model for remoxipride after intravenous and intranasal administration. Drug Metab Dispos. 2011 Dec;39(12):2275-82

IV-31: *Michel Tod* Comparison of the mechanistic static in vivo approach to a PBPK approach for prediction of metabolic drug-drug interactions.

Michel Tod (1), Philippe B. Pierrillas (1), Laurent Bourguigon (2) and Sylvain Goutelle (2)
(1) EMR3738, Université Lyon 1, France, (2) UMR CNRS5558, Université Lyon 1, France

Objectives: Quantitative prediction of the magnitude of a drug-drug interaction (DDI) is useful to identify the clinical interaction studies to be performed during drug development, and the dosing adaptation to be made in the context of drug prescription. Two approaches for quantitative prediction of DDIs mediated by inhibition or induction of cytochromes are the Mechanistic Dynamic interaction Model (MDM) based on in vitro data plugged into a physiologically-based pharmacokinetic model [1], and the Mechanistic Static interaction Model based on in vivo data (IMSM) [2]. The aim of this study was to evaluate the performance of IMSM and to compare IMSM with the MDM approach.

Methods: The magnitude of a pharmacokinetic interaction is usually expressed as the ratio of the victim drug AUC given in combination with an interacting drug (i.e. inducer or inhibitor) to the victim drug AUC given alone. The predictive performances of IMSM (implemented in www.ddi-predictor.org) were evaluated on a panel of 628 clinical sudies of DDIs. The predictive performances of IMSM and MDM (implemented in Simcyp software) were compared on a set of 104 clinical sudies of DDIs. The metrics is the fold prediction error, i.e. the predicted AUC ratio / observed AUC ratio.

Results: On the 628 DDIs panel, the IMSM yielded 85% of predictions within 1.5 fold of the observed value. On the 104 DDIs panel, the predictive performances of IMSM were better than those of MDM : median fold error 1 versus 0.86 ($p = 0.02$), interquartile fold error 0.40 versus 0.52 respectively.

Conclusion: The IMSM approach is a quick, inexpensive and simple alternative for the prediction of metabolic interactions mediated by cytochromes. It may be of interest for both drug development and management of DDIs in clinical practice. The IMSM approach works correctly if cytochromes are the main interaction mechanism, and the kinetics of the substrate is (at least approximately) linear. The MDM approach remains the best approach for the prediction of DDIs involving transporters, provided that the PBPK model is correctly specified.

References:
[1] Einolf HJ. Comparison of different approaches to predict metabolic drug-drug interactions. *Xenobiotica*, 37(10-11), 1257-1294 (2007).
[2] Tod M, Nkoud-Mongo C, Gueyffier F. Impact of genetic polymorphism on drug-drug interactions mediated by cytochromes: a general approach. *AAPS J*, 15(4), 1242-1252 (2013).

IV-32: *Bruna Gaelzer Silva Torres* Population Pharmacokinetic Modeling of Ciprofloxacin Free Lung Concentrations in Healthy and Pseudomonas aeruginosa Biofilm Infected Wistar Rats

Bruna G. S. Torres (1), Alexandre Macedo (1), Elisabet Nielsen (2), Lena E. Friberg (2), Teresa Dalla Costa (1)
(1) Pharmaceutical Sciences Graduate Program, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, (2) Department of Pharmaceutical Biosciences, Uppsala University, Sweden.

Objectives: Biofilm is an important virulence factor that allows bacteria to resist host responses and antimicrobials [1]. Although several pharmacodynamic studies have been conducted showing the intrinsic resistance of a bacteria growing in biofilms [2], little is known about antimicrobials disposition in biofilm infections. The purpose of this study was to develop a comprehensive model able to describe the disposition of total plasma and unbound lung ciprofloxacin (CIP) concentrations in healthy and biofilm infected rats leading to a better understanding of the lung penetration in both conditions.

Methods: Study was approved by UFRGS Ethics in Animal Use Committee (24140). A rat model of lung biofilm infection proposed by Johansen & Høiby was used [3]. CIP lung penetration in healthy and infected rats was investigated after the administration of a single *i.v. bolus* dose of 20 mg/kg. Arterial blood and microdialysis (MD) samples were collected at predetermined time points up to 12 h (total of 30 animals and 526 observations). Data were analyzed with nonlinear mixed effect modeling in NONMEM, version 7.3. Microdialysate samples were described by the integral over each collection interval [4] instead using mid point approach, therefore, no assumptions regarding collection time were made.

Results: The model was built in steps, first plasma data was fitted and found to be well described with a three-compartment model with first-order elimination. Infected animals showed a 34% lower plasma clearance. Unbound lung data were thereafter added and the model was expanded to also describe lung penetration. The central compartment was separated into arterial and venous compartments to explain high initial CIP levels achieved in the lung. Lung penetration and distribution was modeled as a two-compartment model structure linked to the venous compartment. Unbound fraction in plasma was fixed to 0.7 (in house MD data) and separate residual error models were used for total plasma and lung data. All parameters were allometrically scaled with the individual rat body weights. Acceptable predictive performance of the final model was confirmed by VPC.

Conclusions: The PK model developed successfully described the plasma and microdialysis data from healthy and infected rats. The inclusion of the separate arterial and venous compartment could account for the discrepancies between plasma and lung concentrations.

Acknowledgements: CNPq and CAPES/Brazil for financial support.

References:
[1] Parra-Ruiz, J. et al., *Antimicrob. Agents Chemother., 54,* 4329 (2010).
[2] Hengzhuang, W., et al., *Antimicrob. Agents Chemother., 55,* 4469 (2011).
[3] Johansen, H. K., HØiby, N. *Handbook of Animal Models of Infection*, 517 (1999).
[4] Tunblad, K., Hammarlund-Udenaes, M., Jonsson, E. N. Pharmaceutical Research, 21, 1698 (2004).

IV-33: *Elena Tosca* Evaluation of a PK/PD DEB-based model for tumor-in-host growth kinetics under anticancer treatment

Elena Maria Tosca (1), Elisa Borella (1), Nadia Terranova (2), Maurizio Rocchetti, Paolo Magni(1)
(1) Department of Electrical, Computer and Biomedical Engineering, University of Pavia, via Ferrata 5, Pavia, I-27100, Italy; (2) Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland.

Objectives: Mathematical models for describing the tumor growth in animals often neglect the relationship between tumor and host organism. To overcome this limitation, a more mechanistic model, based on energy balance between tumor and host, was developed [1]. This PK/PD model, combining the Dynamic Energy Budget (DEB) theory [2] with the Simeoni tumor growth inhibition (TGI) model [3], describes both the dynamics of the tumor-host interaction and the effect of anticancer treatments. Here a slightly revised model formulation and a new implementation are proposed. Moreover, a comparative study on the tumor growth in control groups between the DEB-TGI model and the widely used Simeoni TGI model is presented.

Methods: Data used for model validation refer to xenograft experiments conducted on Harlan Sprague Dawley mice. Average data of tumor weight and mice net body weight were considered for the control and treated groups. The PKs were derived from separated studies. Monolix 4.3.3 was used for model identification, while Simulx was used to confirm the hypothesis emerged from a dynamic system analysis.

Results: First of all, the model was identified on different experimental datasets with the following strategy: 1) physiological parameters of the tumor-free model were estimated on growth data of typical HSD mice; 2) estimated values were used to find the initial value for the energy reserve at the beginning of the experiment; 3) once fixed the tumor-free model parameters and energy initial value, the tumor-related and the drug-related parameters were simultaneously estimated.
The mathematical analysis of the dynamic system showed that, as the Simeoni model, the DEB-TGI model predicts an exponential growth of the tumor in the early phases of its development. The exponential growth rate depends on several model parameters some of them related to the tumor cell lines and other to the host. We investigated also the relationship between the DEB-TGI model parameters and the decreasing of the tumor growth rate.

Conclusions: The tumor-in-host DEB-based model confirmed its good capability in describing tumor growth and host body growth even when an anticancer drug is administered. Moreover, the affinities emerged from the comparative analysis with the Simenoni model provide a possible biological interpretation of the assumptions underlying the Simeoni model unperturbed (control) growth curve.

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

References:
[1] Terranova N., Del Bene F., Germani M., Rocchetti M., Magni P. An energy based model able to describe the effect of anticancer drugs on tumor growth and host body weight. PAGE 23 (2014) Abstr 3176.
[2] Kooijman S. A. L. M. (2000). Dynamic energy and mass budgets in biological systems. Cambridge university press.
[3] M. Simeoni, P. Magni, C. Cammia, G. De Nicolao, V. Croci, E. Pesenti, M. Germani, I. Poggesi, and M. Rocchetti. Predictive pharmacokinetic pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Research, no. 64, pp. 1094–11 101, 2004.

IV-34: *Mira Tout* Rituximab target-mediated elimination is influenced by both baseline antigenic burden and FCGR3A polymorphism in chronic lymphocytic leukemia

Mira Tout (1), Anne-Laure Gagez (2), Stéphane Leprêtre (3), Nicolas Azzopardi (1), Caroline Dartigeas (4), Béatrice Mahé (5), Emmanuelle Ferrand (6), Hervé Maisonneuve (7), Thérèse Aurran (8), Gilles Paintaud (1,9), Guillaume Cartron (2,10), David Ternant

(1) CNRS UMR 7292, Université François Rabelais, Tours, France, (2) CNRS UMR 5235, Université de Montpellier, Montpellier, France, (3) Hematology, Henri Becquerel Center, Rouen, France, (4) Hématologie et thérapie cellulaire, CHRU Tours, Tours, France, (5) Hematology, CHRU Nantes, Nantes, France, (6) Hematology, CHRU Dijon, Dijon, France, (7) Hematology, CHD La Roche sur Yon, La Roche Sur Yon, France, (8) Hematology, Institut Paoli Calmette, Marseille, France, (9) Laboratoire de Pharmacologie-Toxicologie, CHRU Tours, Tours, France, (10) Hematology, CHRU Montpellier, Montpellier France

Objectives: The anti-CD20 monoclonal antibody rituximab is indicated as first-line treatment in chronic lymphocytic leukemia (CLL). Rituximab exhibits time-dependent clearance in CLL [1], possibly because of treatment-related decrease in B-cell burden over time. However, the influence of CD20 antigenic mass on rituximab pharmacokinetics (PK) has never been investigated in CLL. Our study aimed to quantify the effect of both antigenic mass and FcγRIIIA (*FCGR3A*) genetic polymorphism on rituximab PK in CLL patients.

Methods: Patients included in the CLL 2010 FMP trial were randomly assigned to receive 6 FCR (fludarabine, cyclophosphamide, rituximab) cycles every 28 days, with rituximab IV doses of 375 mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2-6 (standard FCR) or a prephase of intensified rituximab course (500 mg on day 0, and 2000 mg on days 1, 8, and 15) followed by 6 FCR cycles every 28 days with 500 mg/m^2 rituximab infusions (dense FCR). Population modeling was applied using Monolix® 4.3.3, where PK was described by a two-compartment model linked to latent B-cell growth. Baseline total burden of CD20 in the circulation ($CD20_{cir}$) and in the lymph nodes ($CD20_{LN}$), as well as *FCGR3A*-V158F polymorphism were tested as covariates on the PK parameters.

Results: A total of 118 patients (55 standard FCR, 63 dense FCR) were included in the analysis. Our model adequately described rituximab serum concentrations, and allowed the quantification of both rituximab endogenous clearance (CL) and target-mediated elimination (k_{deg}). In the final model, k_{deg} increased significantly with $CD20_{cir}$ (p = 8.1x10^{-5}), and was 13-fold greater between extreme $CD20_{cir}$ values ranging from 0.12 x10^{14} to 402.4 x10^{14}. Patients with the *FCGR3A*-V/V genotype had a 4-fold higher k_{deg} than F carriers (V/F and F/F) (p = 8.6x10^{-5}).

Conclusions: This is the first study showing that B-cell burden and *FCGR3A* genotype influence rituximab elimination. The increase in target-mediated elimination with circulating CD20 antigen suggests that patients with high CD20 antigenic burden may benefit from an increase in rituximab doses.

References:

[1] Li J. *et al.* Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. *J Clin Pharmacol* (2012) **52**, 1918–1926

IV-35: *Mirjam Trame* Development of a Mechanism Based Platform to Predict Cardiac Contractility and Hemodynamics in Conscious Dogs

Raja Venkatasubramanian (1), Teresa A. Collins (2), Lawrence J. Lesko (1), Jay T. Mettetal (3), Mirjam N. Trame (1)

(1) Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA; (2) Drug Safety and Metabolism, AstraZeneca, Cambridge, UK; (3) Drug Safety and Metabolism, AstraZeneca, Waltham, Massachusetts, USA

Objectives: Cardiovascular safety is one of the most frequent causes of safety related attrition both pre-clinically and clinically. Much progress has been made in the area of preclinical to clinical translation of QT interval prolongation and Torsades de Pointes (TdP), however, less progress has been made in areas related to contractility and hemodynamic changes from inotropic agents. Our objective was to develop a mechanism based platform to assess drug induced changes in contractility along with hemodynamic end-points routinely measured in dog telemetry studies.

Methods: Data from contractility ($dPdT_{max}$), heart rate (HR), preload (left ventricular end-diastolic pressure; LVEDP) and blood pressure (MAP) were available from dog telemetry studies for atenolol (n=27), albuterol (n=5), L-NG-Nitroarginine methyl ester (L-NAME; n=4), and milrinone (n=4). PPP&D modeling approaches were utilized for the development of PK/PD correlations using FOCEI method in NONMEM 7.3. The model developed by Snelder et al. [1,2] was used as a starting point and was adapted to include $dPdT_{max}$ and LVEDP as covariate on $dPdT_{max}$ to correct for preload effect. Diurnal rhythms were tested on $dPdT_{max}$, HR, and MAP. Separate drug effects for all drugs included in this analysis were evaluated using linear and (sigmoid) E_{max} relations on $dPdT_{max}$, HR and/or TPR. Nonparametric bootstrap (n=1000) was performed to assess model robustness.

Results: A Population PK model was developed for atenolol and milrinone using available PK data from dog studies and literature data [3,4], while for albuterol and LNAME PK, earlier developed models [5,6] in dogs were used. Diurnal variations for $dPdT_{max}$ and MAP were captured using a single 24h cosine rhythm, while two (24&6h) cosine rhythms were required for HR. Drug effects of atenolol, albuterol, LNAME and milrinone were included on either $dPdT_{max}$, HR and/or TPR capturing the drug effects adequately well for all studies. Incorporation of LVEDP on $dPdT_{max}$, using a time-varying linear covariate model was found to be significant and resulted in ~11% correction of $dPdT_{max}$ for every 10 mmHg LVEDP. Bootstrap analysis obtained adequate model robustness with comparable mean values of parameter estimates to the final model.

Conclusions: The developed mechanism based platform can be used to simultaneously capture drug induced changes in $dPdT_{max}$ along with other hemodynamic end-points, HR and MAP, for multiple drugs in order to assess the hemodynamic safety profiles.

References:

[1] N. Snelder et al., “Drug Effects on the CVS in Conscious Rats: Separating Cardiac Output into Heart Rate and Stroke Volume Using PKPD Modelling,” British Journal of Pharmacology 171, no. 22 (2014)
[2] N. Snelder et al., “PKPD Modelling of the Interrelationship between Mean Arterial BP, Cardiac Output and Total Peripheral Resistance in Conscious Rats,” British Journal of Pharmacology 169, no. 7 (2013)
[3] James McAinsh and Brian F. Holmes, “Pharmacokinetic Studies with Atenolol in the Dog,” Biopharmaceutics & Drug Disposition 4, no. 3 (1983)

[4] J. Edelson et al., “High-Performance Liquid Chromatographic Analysis of Milrinone in Plasma and Urine. Intravenous Pharmacokinetics in the Dog,” Journal of Chromatography 276, no. 2 (1983)
[5] Eleanor Howgate, “Cross-Species Scaling of Cardiovascular Safety Pharmacology Using PKPD Modelling and Simulation,” Thesis, Univ. of Manchester, (2013)
[6] B. Auclair et al., “A Population Analysis of Nebulized (R)-Albuterol in Dogs Using a Novel Mixed Gut-Lung Absorption PK-PD Model,” Pharmaceutical Research 17, no. 10 (2000)

IV-36: *Iñaki F. Trocóniz* Markov Model for Lithium Compliance Assessment

Perez-Castello, I(1); Mangas-Sanjuan, V(2,3); Gonzalez-Alvarez, I(2); Marco-Garbayo, JL(1); Troconiz, I(3); Bermejo, M (2)
(1) Hospital of Gandia; (2) Pharmacokinetics and Pharmaceutical Technology Area, Miguel Hernandez University; (3) Pharmacometrics and Systems Pharmacology. University of Navarra

Introduction: Lithium is an antidepressant used as primary treatment for the prevention of episode recurrences in bipolar disorder, acute treatment of mania and to a lesser extent depression. The main objective of this work is to predict the individual compliance per treatment cycle of the population using a Markov model [1].

Methods: 96 psychiatric patients were enrolled in this study. Lithium carbonate was administrated to all patients at different dose levels (200, 300, 400, 600 and 800 mg) and administration intervals (8, 12 and 24 h). Patients received several treatment cycles and one plasma concentration measurement for each patient was obtained always before starting next cycle (pre-dose) at steady state. Lithium concentrations were categorized below (0), within (1) and above (2) the therapeutic interval. Experimental data were fitted using non-linear mixed-effects modelling implemented in NONMEM 7.2. Different approaches were implemented in order to capture the concentration profiles observed: (1) IOV on bioavailability dose fraction (F1), (2) Markov model on F1 based on the previous categorical lithium state. Model selection was based on the lowest and significant OFV, final parameter estimates and RSE. Model evaluation of the number of (i) transitions per cycle, (ii) transitions per individual or (iii) total number of transitions were performed.

Results: Plasma observations were described using a two-compartment model. Creatinine clearance (CrCl) was selected as significant covariate on typical clearance parameter with a power relationship. The empirical model including IOV on F1 allows for a adequate description of the data. The number of predicted transitions was greater than experimentally observed. A Markov model including the drug compliance on F1 was successfully applied. Markov model predicted more precisely the number of transitions, number of transitions per cycle and number of transitions per individual compared to IOV model.

Conclusions: The final model was able to characterize the number of individuals/observations out of the therapeutic interval with more precision compared to the other approaches proposed.

Reference:
[1] Troconiz IF, et al. Modelling overdispersion and Markovian features in count data. JPKPD. 2009.

IV-37: *Max Tsai* Modelling of Pharmacokinetics and the Incidence of Adverse Events of the PDE-10A Inhibitor TAK-063

Max Tsai (1), Paul Goldsmith (2), Jinhui Xie (1), Tom A. Macek (1)
(1) Takeda Development Center Americas, Inc., Deerfield IL, USA; (2) Takeda Development Center Europe, Inc., London, UK

Objectives: TAK-063 is a potent and selective inhibitor of the phosphodiesterase 10A enzyme expressed primarily in the striatal medium spiny neurons of the basal ganglia and may have therapeutic benefit in treating schizophrenia. Here we describe the modelling of TAK-063 PK and its relationship with adverse events (AEs) observed in Phase 1 studies.

Methods: Data were pooled from two (single and multiple dose) Phase 1, randomised, double-blind, placebo-controlled studies in healthy (Japanese and non-Japanese) subjects and those with schizophrenia (multiple dose only). Following single or daily dosing of TAK-063 or placebo for 7 days, safety and tolerability assessments and PK samples were collected.

1- or 2-compartment model with 1st order absorption and linear or saturable elimination were evaluated as candidate models. Intersubject and residual variability were estimated using various error models. Baseline covariates such demographics, creatinine clearance and disease status (healthy vs schizophrenia subjects) were evaluated using stepwise forward addition and backward elimination.

Incidence of most frequently reported AEs (somnolence and extrapyramidal symptoms [EPS]) was based on a logistic regression model: $f[P(AE_i=1)]=\log[p/(1-p)] = \beta + f_{exp}$ where AE_i =1 if $subject_i$ has AE at some time during the study and 0 otherwise; β = logit for subjects not on drug (placebo); and f_{exp} = function describing the exposure-response relationship expressed as linear or nonlinear forms.

Modelling was conducted using NONMEM or R.

Results: TAK-063 PK was best characterised using a transit compartment model for absorption and a 1-compartment model for disposition. Oral bioavailability was dose-dependent and decreased with increasing dose. A proportional increase in central volume of distribution with BMI was noted; no other covariates were statistically significant. Model demonstrated a reasonable goodness-of-fit.

The frequency of somnolence and EPS appeared to increase with increasing dose and/or exposure. Linear models demonstrated adequate goodness-of-fit with no substantial model improvement using E_{max} function. Disease status as a covariate was significant for EPS but not for somnolence.

Conclusions: The incidence of EPS and somnolence increased with increasing exposure to TAK-063, though a non-zero event rate was noted in placebo subjects. The reason for EPS difference at same doses between healthy subjects and those with schizophrenia requires further investigation.

IV-38: *Ken-ichi Umehara* Assessment of DDI potential of ruxolitinib (INC424), a dual substrate of CYP3A4 and CYP2C9, using a verified PBPK model to support submissions to Health Authorities

Kenichi Umehara (1), Felix Huth (1), Kim Crewe (2), Karen Rowland-Yeo (2) and Gian Camenisch (1)
(1) Novartis Pharma AG, Basel, Switzerland, (2) Simcyp Limited (A Certara Company), Sheffield, UK

Objectives: With the physiologically-based pharmacokinetic (PBPK) model, the drug-drug interaction (DDI) potential of ruxolitinib for CYP3A4 and CYP2C9 was evaluated at the recommended doses in the drug prescribing label.

Methods: Simcyp software (V15) was used. Fractions metabolized by CYP enzymes (fm,CYP) calculated from *in vitro* phenotyping data in the initial ruxolitinib model were revised to the optimized *in vivo* fm,CYP - i.e. estimated based on the clinical DDI study results with ketoconazole. The verified model was used to simulate DDI effects of erythromycin, rifampicin and fluconazole. The CYP2C9 Ki in the original fluconazole model was updated from 7.92 µM to 20.4 µM to capture the clinical DDI effects on the probe substrates of CYP2C9.

Results: The initial ruxolitinib model based on *in vitro* fm,CYP3A4 (0.75) and fm,CYP2C9 (0.19) over-estimated AUC increase with ketoconazole (2.92-fold), compared to the observed ratio (1.91) [1]. With optimized fm,CYP3A4 (0.54) and fm,CYP2C9 (0.40), the predicted AUC ratio was 1.98. The DDI effects of erythromycin and rifampicin on ruxolitinib were well-predicted. The AUC increase with fluconazole (100-400 mg p.o., q.d.) was estimated to be 1.72-3.40-fold using the updated fluconazole model.

Conclusions: Verification of PBPK models by e.g. fm,CYP optimization is an important step to justify dose recommendations or substitute DDI studies. FDA accepted the current model, which was used for the dose adjustment for co-administration of a strong CYP3A inhibitor as ketoconazole, and a dual inhibitor for CYP3A4 and CYP2C9 as fluconazole.

References:
[1] Shi JG, Chen X, Emm T, Scherle PA, McGee RF, Lo Y, Landman RR, McKeever EG Jr, Punwani NG, Williams WV, Yeleswaram S. The effect of CYP3A4 inhibition or induction on the pharmacokinetics and pharmacodynamics of orally administered ruxolitinib (INCB018424 phosphate) in healthy volunteers. J Clin Pharmacol (2012) 52(6):809-18.

IV-39: *Moreno Ursino* Evaluating phase I studies in small populations when incorporating pharmacokinetic information

Moreno Ursino (1), Sarah Zohar (1), Frederike Lentz (2), Corinne Alberti (3), Tim Friede (4), Nigel Stallard (5) and Emmanuelle Comets (6,7)

(1) INSERM, UMRS 1138, team 22, CRC, University Paris 5, University Paris 6, Paris, France, (2) Federal Institute for Drugs and Medical Devices, Bonn, Germany, (3) INSERM, UMR 1123, Hôpital Robert-Debré, APHP, University Paris 7, Paris, France, (4) Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany, (5) Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, The University of Warwick, UK, (6) INSERM, CIC 1414, University Rennes-1, Rennes, France, (7) INSERM, IAME, UMR 1137, University Paris Diderot, Paris, France.

Objectives: To highlight the benefits of conducting a sequential adaptive dose-finding clinical trial by adding information given by PK measurements. We compared several methods for dose selection, including or not PK data, by looking at the percentage of selection of the maximum tolerated dose (MTD). We evaluated whether taking into account PK information brings any benefit.

Methods: The objective phase I dose-finding studies in oncology of is to determine the MTD while limiting the number of patients exposed to high toxicity. Several Bayesian methods to estimate probability of toxicity were compared through simulations. Of the six methods we tested, some estimate the probability of toxicity directly versus dose, others instead estimate the probability of toxicity passing through the AUC. AUC is treated as covariate for the link function of probability of toxicity and/or as dependent variable in linear regression versus dose.
For simulation, we assumed toxicity to be related to AUC and considered 6 possible dose levels.
We simulated trials based on a model for the TGF-β inhibitor LY2157299 in patients with glioma [1]. The PK model was reduced to a one-compartment model with first-order absorption as in [2]. Toxicity occurred when AUC was above a given threshold. For each scenario, 7 in total, we simulated 1000 trials with 30 patients to 60. We evaluated the ability of each method to estimate the dose-toxicity relationship by considering the estimate of the probability of toxicity for each tested dose.

Results: Methods which incorporate PK measurements had comparable performance to those without PK data in terms of percentage of MTD selection. Regarding the ability to estimate the dose-toxicity relationship, looking at the credible intervals built by the first and the third quartile, all the methods are able to estimate properly the probability of toxicity at MTD and at adjacent doses in each scenario; however, only methods which includes PK as a dependent variable are able to estimate adequately the probability associated to all the doses.

Conclusions: Incorporating PK values did not alter the efficiency of estimation of MTD but it increased the ability to estimate the entire dose-toxicity curve. This aspect is very important in case of data extrapolation for further clinical trials.

References:

[1] Gueorguieva, I., Cleverly, A. L., Stauber, A., Pillay, N. S., Rodon, J. A., Miles, C. P., Yingling, J. M. and Lahn, M. M. (2014). Defining a therapeutic window for the novel TGF-β inhibitor LY2157299 monohydrate based on a pharmacokinetic/pharmacodynamic model. British Journal of Clinical Pharmacology, 77: 796 - 807.
[2] Lestini G., Dumont C., Mentré F. (2015). Influence of the size of cohorts in adaptive design for nonlinear mixed effects models: An evaluation by simulation for a pharmacokinetic and pharmacodynamic model for

a biomarker in oncology. Pharmaceutical Research, 32(10): 3159 - 3169.
Acknowledgments: This research has received funding from the European Union's Framework Programme for research, technological development and demonstration under grant agreement no 602144. This work was part of the InSPiRe project but does not necessarily represent the view of all InSPiRe partners.

IV-40: *Muhammad Usman* Population Pharmacokinetics of Meropenem in Elderly Patients: Dosing simulations based on Renal Function

Muhammad Usman and Georg Hempel
Institute of Pharmaceutical and Medicinal Chemistry - Clinical Pharmacy, University of Muenster, Corrensstr. 48, 48149 Muenster, Germany.

Objectives: The aim of this study was to develop a population pharmacokinetic (POPpk) model of meropenem in elderly patients to observe the influence of different covariates on meropenem clearance (CL) and to simulate different dosage regimens in order to observe the percentage probability of target attainment (PTA %) for the plasma concentration of meropenem above MIC of *Enterobacteriaceae, Acinetobacter* Spp. & *Pseudomonas* Spp. in relation with renal function.

Methods: The data of patients above 65 years of age treated with meropenem was collected from different sources [1, 2] and consolidated to form a pooled dataset of 178 patients with 493 samples. A POPpk model was developed by using NONMEM® and influence of different covariates on meropenem CL was observed by stepwise covariate modelling. Monte Carlo Simulations of different dosage regimens with daily dose of 3000 mg at steady state were performed to observe the PTA(%) for maintaining the plasma concentration of meropenem above MIC. The targets for T>MIC were 40%, 60% and 80% of dosage intervals using 1000 virtual patients with 5 different levels of CL_{CR}. The simulated dosage regimens were evaluated across the MIC range of 0.25-128 mg/L and the MIC value for which the PTA was ≥ 90% was considered as PK/PD breakpoint.

Results: The data was best described by a two-compartment model with first-order elimination. The values of population parameter estimates for CL, V_1, Q and V_2 were 5.71 L/h, 14.2 L, 11.8 L/h and 11.2 L respectively. The CL_{CR} and body weight had a significant influence on meropenem CL which is described in final model as CL (L/h) = 5.71×[(1+0.0128)×(CL_{CR}-40.5)×(1+0.0044)×(WT-75)]. The PK/PD breakpoint for 24 h continuous infusion (CI) was 4 mg/L for all the targets of %T>MIC while extended infusions had PK/PD breakpoint one dilution greater than corresponding short infusion regimens for each target of %T>MIC. A 24 h CI was also suitable for maintaining the plasma concentration above MIC of susceptible, intermediate and resistant strains of target bacteria for the entire duration of dosage interval and the levels of CL_{CR} ≥ 100 mL/min.

Conclusions: It is concluded that 3000 mg of meropenem administered over 24 h CI is effective against moderate to severe infections caused by susceptible, intermediate and resistant strains of target bacteria for CL_{CR} level of ≥ 100 mL/min. However, higher dose of meropenem would be required for resistant strains if CL_{CR} is approaching to 200 mL/min.

References:
[1] Doh, K., et al., *Population pharmacokinetics of meropenem in burn patients.* J Antimicrob Chemother, 2010. **65**(11): p. 2428-35.
[2] Isla, A., et al., *Population pharmacokinetics of meropenem in critically ill patients undergoing continuous renal replacement therapy.* Clin Pharmacokinet, 2008. **47**(3): p. 173-80.

IV-41: *Vladimir Vainstein* Dose translation of a hematopoietic acute radiation syndrome protection agent (recombinant human Interleukin-12) to humans.

Martin Beliveau(1), Claudia Jomphe(1), Zoya Gluzman-Poltorak(2), Lena Basile(2), Vladimir Vainstein(2)
(1) Certara Strategic Consulting, Montreal, Canada (2) Neumedicines Inc Los Angeles US

Objectives: Acute radiation syndrome (ARS) is a life-threatening illness caused by whole body or significant partial-body exposure to radiation doses > 1 Gy over a short period of time, as would occur in the event of a nuclear accident or attack. The development program for rHuIL-12 (HemaMax) as a medical countermeasure to lethal radiation exposure follows the FDA's Animal Rule, where efficacy is determined in appropriate animal models and safety is demonstrated in humans. Because the effective human dose cannot be assessed in controlled clinical efficacy studies due to ethical issues, HemaMax was translated by combining the animal and clinical data into a translational modeling dose scaling approach to address animal rule requirements.

Methods: PK data from HemaMax IV and SC administration in non-human primate and healthy human volunteer trials were analyzed by non-compartmental analysis, as well as by modeling drug disposition in population approach. Absorption of HemaMax following sub-cutaneous (SC) dosing was optimized by including two parallel, first-order absorption processes to account for the absorption via the lymphatic system and blood capillaries. The effect of irradiation on pharmacokinetics was also investigated. Population analysis was used to evaluate exposure in the typical US population in case of radiation disaster.

Results: Data analysis suggested that irradiation had minimal impact on actual exposure metrics and that exposure to HemaMax was similar in irradiated and non-irradiated monkeys. Monte Carlo simulations demonstrated that HemaMax SC doses ranging from 150 to 250 ng/kg in non-irradiated monkeys resulted in more than 90% of exposure being within those observed in non-irradiated humans administered a 12 µg SC dose. As such, due to species differences and variability observed in PK, an efficacious HemaMax dose of 150 ng/kg in non-irradiated monkeys would correspond to a human dose of 12 µg. Analysis of the covariates established that in case of unit dose administration weight contributes only about 20% variability in the systemic exposure.

Conclusions: modeling of non-human primate and human PK data of HemaMax allowed for successful dose translation between the species and establishment of the projected efficacious dose to support the development of the drug under Animal Rule; PK analysis also supports use of a unit dose, which greatly facilitates emergency use of the drug.

IV-42: *Pyry Välitalo* A mathematical method assessing the informativeness of total test score on the basis of an item response theory model: A case study on pain in children

Pyry A.J. Välitalo(1), Vivi Rottschäfer(2), Monique van Dijk(3), Catherijne A.J. Knibbe(1,4), Elke H.J. Krekels(1)

(1) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands; (2) Mathematical Institute, Leiden University, Leiden, the Netherlands; (3) Department of Pediatric Surgery and Pediatrics, Erasmus MC-Sophia Children's hospital, Rotterdam; (4) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands

Objectives: A composite score of observational scales with multiple items is often used to quantify disease severity. Graded response models (GRM) are a subset of item response theory (IRT) models, where the grades of an item are considered ordered categorical data[1]. In an IRT context, adding items to a test always leads to increased test information about the latent variable. The same may not be true for the total score approach, and total scores may become less informative as the variance of discrimination parameters increases[2]. The objectives of this study were: 1) to derive an equation for total score information, based on GRM parameters and 2) to systematically compare the informativeness of total score approach in various scenarios with simulated and real clinical data on pain in children.

Methods: The information of a continuous variable can be calculated using the first derivative of the variable with respect to a given parameter, and the variance of the variable[3]. This was used as the starting point for the development of the equation for total score information. Subsequently, the test information from total scores approach was compared to test information from GRM modeling approach in a set of 504 simulation scenarios. For the real clinical data, GRM parameters were retrieved from a previous study quantifying the informativeness of items in the COMFORT scale[4]. This is a multi-item observational scale to assess pain in neonates. The contribution of each COMFORT item to the total COMFORT score was evaluated.

Results: The test total score was transformed to a continuous variable, upon which the test information of the total score could be calculated[3]. In simulated scenarios, the total score was always less informative (by 1-39%) than an IRT analysis of the same items. If the GRM parameters were identical for each item, the information of the total score was 96-99% of the IRT test information. If the GRM parameters differed between items, the total score information decreased relative to the IRT test information. The case study showed that COMFORT scale items "Heart rate", and "Blood pressure" decrease the informativeness of the total COMFORT score. Moreover, the influence of COMFORT item "Respiratory response" on the total score informativeness was minimal.

Conclusions: The equation can be used to assess the impact of individual items on the overall informativeness of clinical observational scales, enabling the optimization of such scales by exclusion of uninformative items.

References:

[1] Samejima F. Psychometrika 1970;35:139–139.
[2] Schindler E. et al. PAGE 24 (2015) Abstr 3468.
[3] Lehmann E. Theory of Point Estimation. John Wiley & Sons, 1983.
[4] Välitalo P. et al. Pain 2016 Jan 5 [epub ahead of print]

IV-43: *Willem van den Brink* Finding underlying longitudinal patterns in pharmaco-metabolomics data

W. van den Brink, R. Hartman, M. de Bruin, B. Gonzalez, J. Elassaiss-Schaap, P.H. van der Graaf, T. Hankemeier, E.C.M. de Lange
Leiden Academic Centre for Drug Research, Leiden University, The Netherlands

Objectives: To develop a method that integrates multidimensional pharmaco-metabolomics data into a single PKPD systems pharmacology model in a data-driven manner, ultimately to reveal the underlying patterns in the pharmaco-metabolomics response.

Methods: Pharmacological experiments were performed in which 0, 0.7 or 3.5 mg/kg remoxipride was administered to rats. Plasma samples were obtained over a period of 4 hours and were subsequently analysed for biogenic amines using a metabolomics approach as described previously [1]. PKPD turnover models were developed for the pharmacodynamic response of each single metabolite using NONMEM V7.3.0 [2]. The PK parameters were fixed to those identified in an earlier study (not published). Principal component analysis was applied to the dataset with the model parameters as variables and the metabolites as individuals in order to reveal clusters of metabolites. Kmeans clustering was performed to identify the cluster means, which were subsequently used to inform on the structure towards a 'whole system model'.

Results: 44 metabolites were analysed in plasma and most of these showed a dose dependent decrease after remoxipride administration. A type I turnover model (inhibiting effect on k_in) with an Emax drug effect model, was identified for each single metabolite. 'Whole system' models with 4, 5 and 6 clusters as identified by kmeans were compared, 5 clusters being the optimal number of clusters with a significant drop in OFV as compared to 4 clusters (-104 points), and no significant difference with 6 clusters (+2 points).

Conclusions: A methodology was developed for finding underlying patterns in pharmaco-metabolomics data. 5 different longitudinal patterns were identified in 44 metabolite profiles, all of which could be described by type I turnover models.

References:
[1] Noga MJ, Dane A, Shi S, Attali A, van Aken H, et al. (2012) Metabolomics of cerebrospinal fluid reveals changes in the central nervous system metabolism in a rat model of multiple sclerosis. Metabolomics 8(2): 253–63
[2] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2013. Icon Development Solutions, Ellicott City, Maryland, USA.

IV-44: *Sven van Dijkman* Differentiation between Parkinson's and Parkinson's-like patients in MDS-UPDRS-based diagnosis

Sven C. van Dijkman (1), Gopichand Gottipati (1), Elodie L. Plan (1), Mats O. Karlsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: It has been shown in the PPMI study [1] that approximately 15% of patients with MDS-UPDRS scores suggesting Parkinson's disease (PD) are later found to not show dopaminergic deficits on a SPECT scan (SWEDD cohort). For confirmed PD patients (DeNoPD cohort), an Item Response Theory (IRT) model (DeNoPD model) was previously built on the MDS-UPDRS individual item scores. Here, it was our aim to determine if patient type differentiation could be performed by expanding the DeNoPD model to SWEDD patients.

Methods: Data used in this work were obtained from the Parkinson's Progression Markers Initiative (PPMI) database [1] A SWEDD model was developed based on the DeNoPD model and a shift parameter for each UPDRS item, estimated on the SWEDD data alone. Based on ratios of individual likelihoods from evaluating both models on screening and baseline data of both cohorts, the probability of belonging to either cohort could be estimated for each patient. Differentiation power residing in individual items was assessed using subsets of individuals´ data, by an iterative item addition process.

Results: IRT model based differentiation between PD and PD-like patients was found to be 86.3% sensitive and 62.7% specific to detecting PD. A subset of 14 items was found to be 94.9% sensitive and 57.8% specific compared to the full 68 item MDS-UPDRS rating scale for differentiation of these patients.

Conclusions: The proposed model allows a distinction between PD and PD-like patients to be made to a higher degree of sensitivity and similar specificity compared to visual clinical examination [2], while avoiding the need for expensive and burdensome radiological testing such as SPECT or MRI scans.

References:
[1] The Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org
[2] Bajaj NPS, Gontu V, Birchall J, Patterson J, Grosset DG, Lees AJ. Accuracy of clinical diagnosis in tremulous parkinsonian patients: a blinded video study. J Neurol Neurosurg Psychiatry. 2010;81:1223–8

IV-45: *Tamara van Donge* Evaluating biosimilarity of monoclonal antibodies: comparison of population approach nonlinear mixed effects models to standard non-compartmental analysis

J.A.A. Reijers (1), T. van Donge (1), F.M.L. Schepers (1), J. Burggraaf (1), J. Stevens (1)
(1) Centre for Human Drug Research (CHDR), Leiden, The Netherlands

Objectives: To study pharmacokinetic biosimilarity using full concentration-time profiles from a population pharmacokinetic analysis of 2 biotherapeutics (trastuzumab) and compare the results to a standard non-compartmental analysis (NCA) that uses the observed concentration-time points.

Methods: The pharmacokinetic data were obtained from a biosimilarity trial (n=110) of trastuzumab in which intravenous doses of 0.49, 1.48, 2.96, 5.96 mg/kg test product and 6.44 mg/kg of reference product were administered to healthy volunteers[1]. Using NONMEM 7.2[2], a combined PK model was developed for the test and reference product, as were two PK models on test and reference product separately. To allow comparison between all models, structural similarity was pursued. Using the resulting individual concentration-time profiles, AUCs were calculated using linear trapezoidal rule. Then, using the observed concentration-time data, standard NCA methods were used to calculate the individual AUCs, which were compared to the model results.

Results: The PK of trastuzumab was best described using a three compartment model with combined linear- and Michaelis-Menten elimination. Interindividual variability could be identified on three PK parameters. Residual variability was best described by a combined proportional and additive error model. Lean body weight was identified as covariate on central volume of distribution and body mass index on the elimination rate constant. Trastuzumab product could not be identified as a significant covariate on any parameter. The geometric mean ratio (GMR, 95% confidence interval) of the AUC_{inf} of the test/reference product for combined model was 81.66% (77.93-85.56%). For the separate models, GMR was 82.54% (78.70-86.57%). Following NCA, the GMR of the AUC_{inf} was 82.32% (78.17-86.69%). After standard linear dose correction for the labelled dose of 6 mg/kg using separate model results, GMR for the AUC_{inf} was 91.74% (87.46-96.24%) for population pharmacokinetic analysis and 89.55% (85.03-94.30%) for the NCA.

Conclusions: The obtained AUCs of the developed PPK models were comparable to the NCA results, regardless whether test and reference product were modelled in one combined or two separate models. Previously, the interchangeability of PPK models in biosimilarity research has been proven for therapeutic proteins[3]. We show that this also applies for the relatively large monoclonal antibody trastuzumab which displays non-linear pharmacokinetics.

References:

[1] Wisman LA, De Cock EP, Reijers JA, Kamerling IM, Van Os SH, de Kam ML, Burggraaf J, Voortman G. A phase I dose-escalation and bioequivalence study of a trastuzumab biosimilar in healthy volunteers. Clinical Drug Investigation (2014) 34:887-894.
[2] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.
[3] Dubois A, Gsteiger S, Balser S, Pigeolet E, Steimer JL, Pillai G, Menté F. Pharmacokinetic similarity of biologics: Analysis using nonlinear mixed-effects modeling. Clinical Pharmacology &Therapeutics (2012) 91(2): 234-242.

IV-46: *MJ Van Esdonk* Development of a semi-population deconvolution method for the analysis of growth hormone profiles

M.J. van Esdonk (1,2), J. Stevens (2), P.H. van der Graaf (1), J. Burggraaf (1,2)
(1) Systems Pharmacology, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands. (2) Centre for Human Drug Research, Leiden, The Netherlands.

Objectives: A major disadvantage of standard deconvolution techniques is that the variable time is not taken forward in the analysis. Therefore, an integrated semi-population deconvolution method was developed to study the endogenous profile of growth hormone (GH) as a first step to better understand the pharmacodynamics of drugs targeting the secretion of GH.

Methods: This clinical trial consisted of 8 healthy and 16 obese female volunteers in which 24 hour GH profiles were measured at 10 minute sampling intervals. With deconvolution techniques, pulsatile data, such as GH profiles, can be analyzed and secretion parameters can be estimated (frequency of pulses, amplitude of pulses, etc.). AutoDecon [1], a fully automated deconvolution program, was used for the individual deconvolution analysis of the GH profiles. The deconvolution output was used in NONMEM 7.3 [2] for the development of a semi-population model in which individuals could retain their individual secretion profiles combined with the estimation of population parameters. Simulations of inhibiting and stimulating pharmacodynamic effects targeting the growth hormone secretion parameters were performed.

Results: The semi-population model was able to fit the data by defining each peak as a different occasion. Peaks were modelled as Gaussian shaped events being released in a 1 compartment model with a first order elimination. The population parameters in this model were the baseline secretion rate, secretion pulse width, secretion pulse amplitude and the growth hormone elimination rate constant. The pulse interval could not yet be implemented as a population parameter in this model structure.

Conclusions: Using the semi-population deconvolution method developed in this study, GH-profiles can be followed over time and the differences in growth hormone secretion between groups can be quantified. The simulations performed with the current model showed that it could be used to model scenarios that cannot not be identified by solely using traditional deconvolution analysis. The analysis method that has been developed in this study provides the opportunity to concurrently model the pharmacokinetics and pharmacodynamics of drugs that target the secretion of growth hormone.

References:
[1] MJ Johnson, L Pipes, PP Veldhuis, et al. AutoDecon: A Robust Numerical Method for the Quantification of Pulsatile Events. Methods Enzymol (2010). 454: 367–404.
[2] Beal SL, Sheiner LB, Boeckmann AJ, and Bauer RJ (eds) NONMEM 7.3.0 Users Guides. (1989–2013). ICON Development Solutions, Hanover, MD.

IV-47: *Coen van Hasselt* The proof is in the pee: Population asparagus urinary odor kinetics.

J. G. Coen van Hasselt(1), Jeroen Elassaiss-Schaap(1,2), Anuradha Ramamoorthy(3), Brian M. Sadler(4), Sreeneeranj Kasichayanula(5), Yin Edwards(6), Piet H. van der Graaf(1,7), Lei Zhang(1), John A. Wagner(8)
(1) Leiden University, Leiden, Netherlands; (2) PD-Value BV, Houten, Netherlands; (3)Food and Drug Administration, Silver Spring, MD, USA; (4)ICON, Gaithersburg, MD, USA; (5)Amgen, Thousand Oaks, CA, USA; (6)ICON plc, Marlow, UK; (7)Certara, Canterbury, UK; (8)Takeda Pharmaceuticals International Co., Cambridge, MA, USA.

Objectives: Inter-individual variability (IIV) in production and perception of odorous urine after eating asparagus has been reported [1]. We conducted a “first-ever” clinical study with consenting 2014 and 2015 ASCPT annual meeting attendees to characterize asparagus urinary odor kinetics. The objective of this study was to characterize time-response, dose-response dynamics and half-life (t½) of urinary asparagus odor perception after receiving a single variable dose of asparagus.

Methods: Consenting subjects were randomized to eat a specific number (dose) of asparagus spears. Subjects were asked to report their urinary odor perception for until no noticable odor was perceived on case report forms. Odor perception was reported as a subjective score on a scale of 0-6 (0=no odor to 6=offensive odor). A mixed effect proportional odds K-PD model was used to associate dose with odor scores, and to estimate a t½ for dose received. A mixture model was used to estimate the proportion of responders (P_{RESP}) in terms of perceiving and/or producing the odor in urine. An asparagus dose-response slope parameter was considered in the proportional odds model as additional term.

Results: Data was pooled from a pilot study (n=10; dose 0, 5, 10, 15 spears), and the main study (n=81; dose 0, 3, 6, 9 spears). Out of these 91 subjects, 9 reported no detectable odor. A half-life of 3.9 h (RSE, relative standard error, 44%) was estimated. A dose-response slope term was identified with good precision (22%), and was found to be equal for different score levels. For scores 4 and 5, a single coefficient was estimated due to insufficient data. IIV was estimated for t½ and for baseline variability of the score for responders. IIV on the t½ and baseline parameter was large: 43.4 CV% and 84.3 CV% respectively. P_{RESP} was estimated at 92.4% (RSE 12%). A correlation between age and t½ was present but could not be reliably included in the model.

Conlusion: Dose-response dynamics of asparagus urinary odor score and time course data could be adequately characterized using the developed model. There was large IIV in asparagus t½ and baseline score. This study design can be used as a demonstration project for population kinetics studies in many settings including schools. We plan to build a tutorial and an open sourced database with the potential to link results through “crowd sourcing” and allowing other researchers to add their data and build the database.

References:
[1] Drug Metab Dispos. 2001 Apr;29(4 Pt 2):539-43.

IV-48: *Filippo Visco Comandini* Competitive brain and body growth model

Jason Cawley, Filippo Visco Comandini
Wolfram Solutions

Objectives: Malnutrition has a considerable effect on the body development during childhood and, in particular, it affects brain development and cognitive abilities. In case of undernutrition, there is a competition for limited energy resources in the rapidly growing and maturing body, between the development of the brain and the development of the rest of the body.

Methods: We propose a mathematical model that links the daily nutrient intakes to brain and body development. The model characterizes normative infant growth curves and is able to simulate different scenarios like regular feeding, catch-up growth and under- and over-nutrition based on changes in nutritional intake. Available energy generated from varied nutrient intake are assigned to different reservoirs (brain maintenance and its development, body maintenance and its development and physical activity). In case of underfeeding and malnutrition, these reservoirs will compete for the caloric resources.

Results: We first successfully characterized the normative growth curves associated with each percentile "growth channel" of the WHO standard growth curves. We subsequently used the model to estimate the daily nutrient intakes for the first 5 years of a longitudinal Guatemala study (N =92).

Conclusions: The proposed brain and body predation growth model provides a framework for mechanistic exploration of anthropometric outcome and permits evaluations of different scenarios driven by nutrient intakes, such as regular feeding, malnutrition, and required caloric intake to support catch-up growth.

References:
[1] Butte Nancy Energy requirement of infants,Public Health Nutrition. - 2005. - 7A : Vol. 8. - pp. 953-967 .
[2] Dekaban Anatole and Sadowsky Doris Changes in Brian Weights during the span of human life: relation of brain weights to body heights and body weights , Annals of Neurology. - 1978. - Vol. 4. - pp. 345-356.
[3] Hazhir Rhamandad Human Growth and body weight dynamics: an integrative systems model, PloS one. - 2014. - 12 : Vol. 9. - p. e114609.
[4] Kuzawa Christopher [et al.] Metabolic costs and evolutionary implications of human brain development, Proceedings of the National Academy of sciences. - 2014. - 36 : Vol. 111. - pp. 13010-13015

IV-49: *Swantje Völler* Dose Recommendations for Recombinant Asparaginase in Children: A Population Pharmacokinetic Analysis

Swantje Völler (1) *, Uwe Pichlmeier (2), Gudrun Würthwein (1), Georg Hempel (1)
*(1) Institute of pharmaceutical and medicinal Chemistry, Clinical Pharmacy, Westfälische Wilhelms-Universität Münster, Germany, (2) medac, Gesellschaft für klinische Spezialpräparate mbH, Hamburg, Germany, *current address: LACDR Leiden, Faculty of Science, Universiteit Leiden, The Netherlands*

Objectives: The enzyme Asparaginase is used for remission induction and post-induction treatment in acute lymphoblastic leukemia. A new recombinant E.coli-Asparaginase (rASNase) was developed by medac GmbH (Wedel, Germany) and recently approved by the EMA. Bio analytical data originated from three clinical studies in children (EudraCT numbers: 2004-003785-16, 2006-003180-31, 2008-006300-27) was available for population pharmacokinetic (popPK) analysis.

Methods: A popPK model for rASNase was developed using NONMEM® 7.2 and a predefined step-by-step model building process. During treatment trough activity of rASNase should be maintained above 100 U/L to keep serum asparagine levels undectecable. Based on simulations of the popPK model, different dose adjustments were investigated for their ability to increase rASNase trough activities in those patients affected by low through activities.

Results: One hundred twenty-four children with previously untreated acute lymphatic leukaemia were included in the analysis. Model-building resulted in a two compartment model for rASNase (CL=0.154 L/h/70 kg, V1=4.24 L/70 kg, Q=0.801 L/h/70kg, V2=1.13 L/70 kg). Inter individual variability on CL (20.4%) and V1 (20.2%), intra-individual variability of the V1 (12.5%) and residual variability (proportional error 2.25%, additive error 34.7 U/L) were assessed. Allometric scaling with a fixed exponent of 0.75 on weight for CL and Q, and weight on V1 and V2 was used. Further covariates, e.g. liver function, kidney function, fibrinogen or antithrombin III did not influence the model. Simulations suggest that neither doubling the dose nor shortening the dose interval in patients with rASNase trough activities below 25 U/L are likely to result in activities above 100 U/L for the following administrations. For activities between 25 U/L and 50 U/L, it might be useful to reduce the dose interval from every 72h to every 48h. For activities between 50 U/L and 75 U/L, simulations suggest that doubling the dose is an alternative to reducing the dose interval. If the trough activity is between 75 U/L and 100 U/L (d), increasing the dose by 50% appears to be sufficient to reach trough activities above 100 U/L, associated with an acceptable increase in peak activities.

Conclusions: A popPK model describing the PK of rASNase in children was successfully developed and validated. The model can be used to aid dose finding in children affected trough activities below 100 U/L.

IV-50: *Max von Kleist* Systems pharmacology pipeline to assess NRTI-efficacy for repurposing as pre-exposure prophylactic compounds against HIV-1 infection

Sulav Duwal, Vikram Sunkara, Max von kleist
Freie Universität Berlin

Objectives: While HIV-1 cannot be cured, current efforts focus on developing pharmaco-intervention strategies to end the epidemic. Two strategies have been proposed: (i) Treatment-as-prevention (TasP) decreases the patients' virus load and thereby markedly reduces the infectivity of the potential transmitter. However, onwards transmission may preferentially occur early after infection [1], when the potential transmitter is unaware of his/her infection, arguing that TasP may only prevent a small fraction of transmission events in reality. (ii) The second intervention is called pre-exposure prophylaxis (PrEP). Here, an uninfected, exposed individual takes anti-viral drugs to prevent infection upon viral exposure.

Our objective was to use a predictive PK-coupled MOA model for nucleoside reverse transcriptase inhibitors (NRTIs) [2,3] to explore the potential of the NRTIs lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF) for repurposing in the context of PrEP. We assessed the mechanisms of prevention and pharmacological limitations and opportunities for various schedules.

Methods: We developed mechanistic models that relate viral load in the potential transmitter to viral exposure in the recipient and estimated the infection probability for unprotected sex. All steps were validated using published data. We estimated reduction in infection probability under prophylaxis, taking the individual PK of the analyzed NRTIs within the exposed person into account. This pipeline allowed us to analyze the efficacy of all NRTIs, integrating virus load in the transmitter, mode of exposure, timing of viral challenge, and dosing schedule.

Results: The viral load distribution in the potential transmitter population [1] was log-normal distributed. Predictions indicated that FTC and 3TC are superior to TDF, in contrast to current beliefs [4], which was particularly evident for 'PrEP on demand'. Our pipeline revealed a dependency between reported efficacy endpoints in PrEP trials and the individual follow-up duration. This may explain contradicting reports with regard to PrEP efficacy.

Conclusions: We report the first approach to mechanistically model PrEP efficacy by integrating viral loads within the donor population, mode- and timing of viral challenge with respect to PK-PD in the exposed individual. The framework can be extended to other drug classes and also be used explore TasP efficacy with- and without PrEP. Furthermore it can inform epidemiologic models.

References:
[1] Yousef, KP, Meixenberger K, Smith MR, Somogyi S, Gromöller S, Schmidt D, Gunsenheimer-Bartmeyer B, Hamouda O, Kücherer C and von Kleist M (2016) JAIDS (under revision)
[2] von Kleist M, Metzner P, Marquet R and Schütte C (2012) PLoS Comp. Biol. 8: e1002359
[3] Duwal S, von Kleist M (2016) European Journal of Pharmaceutical Sciences, ahead of print doi:10.1016/j.ejps.2016.01.016
[4] Hendrix CW (2013) Cell 155(3):515-8

IV-51: *Camille Vong* Population Pharmacokinetics of Tofacitinib in Induction Studies for Moderate-to-Severe Ulcerative Colitis Patients

Camille Vong (1), Chenhui Deng (2); Rujia Xie (2); Steven W. Martin (1); Dahong Yu (4); Deborah A Woodworth (4); Wojciech Niezychowski (4); Chinyu Su (4); Arnab Mukherjee (3)
Pfizer Inc, (1) Cambridge, MA, United States (2) Shanghai, China (3) Groton, CT, United States (4) Collegeville, PA, United States.

Objectives: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). The objectives of this analysis were to develop a population PK model of tofacitinib using pooled data from Phase 2 and 3 studies and evaluate the possible relationship between exposure and covariates.

Methods: Data from 1054 patients (median age: 41 years; median weight: 74 kg; median baseline Mayo score: 9) receiving tofacitinib either as 0.5, 3, 10 or 15 mg twice daily (BID) were analyzed using FOCE with Interaction in NONMEM. The following patient characteristics were assessed as covariates on PK parameters using a full model approach: race, sex, age, body weight, baseline creatinine clearance, baseline C-reactive protein, baseline albumin, ethnicity and use of concomitant medication (oral steroids and 5-ASA). Single imputation method based on the remaining available data was used for proportion of missing covariates less than 10% (case for all exploratory covariates, except ethnicity that was excluded from the covariate analysis). 4.5% of total concentrations were BLQ and excluded from the analysis. Goodness of fit plots and visual prediction checks were used for model selection and evaluation. Bootstraps were applied to identify significant covariate effects in the full covariate model.

Results: The PK of tofacitinib exhibits linear PK and was best characterized by a one-compartment first-order absorption model with an absorption lag time of 0.23 hr. Mean (RSE %) estimated PK parameters for a typical study subject were apparent clearance (CL/F) of 25 L/hr (1.13), apparent volume of distribution (V/F) of 108 L (1.12) and first-order absorption rate constant (Ka) of 9.31 hr^{-1}(8.63). Correlation between CL/F and V/F was estimated at 0.261. Inter-individual variability (ISV) (RSE %) estimated for CL/F was 24.6 % (8.55) and an Inter-occasion variability (IOV) for Ka was 179% (7.49). The full model included covariate relationships of creatinine clearance and race on clearance while significant covariates for volume were age and body weight.

Conclusions: The proposed model adequately describes tofacitinib plasma PK that was found consistent between phase 2 and 3 studies. This model will be used in the next step to evaluate the exposure-response correlation between tofacinitib exposure and primary and secondary endpoints of remission and mucosal healing at Week 8 (central read) based on Mayo scores.

References:
[1] Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010; 105:501-23.
[2] Meyer DM, et al., Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond). 2010. 11; 7:41.
[3] Murray PJ, The JAK-STAT signaling pathway: input and output integration. J Immunol. 2007. 178(5): 2623-9.
[4] Gastonguay MR, A Full Model Estimation Approach for Covariate Effects: Inference Based on Clinical

Importance and Estimation Precision. Abstract at 2004 AAPS Annual Meeting.

IV-52: *Veronika Voronova* Investigation of the diabetes-related metabolic memory phenomenon using a quantitative systems pharmacology approach

Veronika Voronova (1), Kirill Zhudenkov (1)
(1) M&S Decisions LLC

Objectives: Hyperglycemia is generally associated with an increased intracellular generation of reactive oxygen species (ROS) and oxidative stress. ROS may, in turn, play a key role in the development of various diabetes-related complications. A quantitative link between glucose plasma levels and oxidative stress shows a complex behavior [1]. First, oxidative stress persists after glucose normalization, and this is defined as metabolic memory. Second, instable glucose is more detrimental for living systems comparing to constant high glucose. The objective of the current study was to explain mechanisms of these observations, using an integrative, quantitative systems pharmacology (QSP) modeling approach.

Methods: The model was based on a system of ordinary differential equations and included the following mechanistic and semi-empirical relationships: (a) increased glucose level stimulates ROS generation and oxidative stress, which triggers a process of continuous adaptation to hyperglycemia; (b) excess ROS promotes the accumulation of metabolic memory, which accelerates glucose effect on ROS generation. Model parameters were verified using published *in vitro* data [1], such as ROS generation as measured in endothelial cell cultures placed into constant high (20 or 30 mmol/l) or oscillating (24 h in 5 mmol/l - 24 h in 25 mmol/l) glucose followed by normal glucose (5 mmol/l).

Results: The developed model adequately described data from the literature. It adequately reproduced the metabolic memory phenomenon and predicted excess ROS generation after glucose normalization. This behavior is caused by a system of positive feedback regulations between ROS and cumulative effects of the metabolic memory appearance and adaptation. Additionally, model simulations showed that, *in vitro*, the appearance of metabolic memory is dependent on the duration of cell exposure to glucose levels.

Conclusions: A QSP model describing glucose effects on ROS generation was developed, based on data published in the literature. The model was used to explore the hypothesis of metabolic memory appearance in response to excess ROS and glucose levels. This model can be further used to probe long-term effects of diabetes progression and development of diabetes-related complications.

References:
[1] Quagliaro L, Piconi L, Assaloni R. Intermittent High Glucose Enhances Apoptosis Related to Oxidative Stress in Human Umbilical Vein Endothelial Cells: The Role of Protein Kinase C and NAD(P)H-Oxidase Activation. Diabetes. 52:2795-2804, 2003

IV-53: *Ulrika Wählby Hamrén* Pharmacokinetics of the inhaled selective glucocorticoid receptor modulator AZD5423 following inhalation using different devices

Johanna Melin (1,2,3), Susanne Prothon (3), Charlotte Kloft (1), Adriaan Cleton (4), Carl-Christer Johansson (3), Carin Jorup (5), Bo Olsson (3), Ulrika Wählby Hamrén (3)
(1) Dept Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany

Objectives: AZD5423 is a non-steroidal glucocorticoid receptor modulator, with low aqueous solubility (<1 µM), developed for once daily treatment of asthma and COPD. In this work we aimed to evaluate and compare the absorption pharmacokinetics (PK) of AZD5423 after inhalation via four devices (Spira®, I-neb®, Turbuhaler® and a new dry powder inhaler (new DPI)) in two studies using differently sized primary particles, and to compare the pulmonary bioavailability (Fpulmonary) with the predicted lung deposited dose (according to Olsson [1]).

Methods: Plasma concentration-time data after intravenous, oral and inhaled administration via 4 devices were available from two clinical studies in healthy and asthmatic subjects. A population PK model was developed in a sequential manner, similar to [2-4], with parallel absorption compartments for inhaled AZD5423; a non-compartmental analysis was performed for comparison.

Results: Fpulmonary varied between devices, with the lowest estimates for I-neb (27%) and Turbuhaler (30%) and the highest for the new DPI (46%) and Spira (35%-49%). Fpulmonary were substantially lower than the predicted lung deposited dose (range 57-89%). Lung absorption was separated into a faster and a slower process. The half-life of the faster absorption appeared formulation-dependent, while the slower absorption (half-life of 35-47 min) appeared independent of formulation.

Conclusions: The large difference between the estimated Fpulmonary and the predicted lung deposited dose for AZD5423 in this study is likely caused by a high degree of mucociliary clearance. The low solubility did not result in significant lung retention.

References:

[1] Olsson B, Borgström L, Lundbäck H, Svensson M. Validation of a General In Vitro Approach for Prediction of Total Lung Deposition in Healthy Adults for Pharmaceutical Inhalation Products. J Aerosol Med Pulm Drug Deliv (2013) 26(6):355–69.
[2] Bartels C, Looby M, Sechaud R, Kaiser G. Determination of the pharmacokinetics of glycopyrronium in the lung using a population pharmacokinetic modelling approach. Br J Clin Pharmacol (2013) 76(6):868–79.
[3] Borghardt JM, Weber B, Staab A, Kunz C, Formella S, Kloft C. Investigating pulmonary and systemic pharmacokinetics of inhaled olodaterol in healthy volunteers using a population pharmacokinetic approach. Br J Clin Pharmacol (2015) ; doi: 10.1111/bcp.12780
[4] Melin J, Olsson BL, Johansson C, Kloft C, Wählby Hamrén U, Population pharmacokinetic analysis of AZD4818 in healthy volunteers following three different routes of administration, PAGE 2015

IV-55: *Siyuan Wang* An integrated PK/PD model to link the frequency of cancer-stem-like cells to tumor volume for sunitinib combined with dopamine in the treatment of drug-resistant breast cancer

Siyuan Wang, Xiao Zhu, Tianyan Zhou, Wei Lu
Peking University/Pharmacometrics Education Center, Beijing, China

Objective: Increasing evidence indicates that the contributions of cancer stem-like cells (CSCs) may act as hallmarks of cancer development (1, 2). To simultaneously de-bulk the tumor size and prevent cancer recurrence, it's essential to combine conventional antitumor therapies with CSCs-targeting therapies (3). However, despite documented evidence of the antitumor activity of the combination therapy (4), limited information is available on the quantitative relationship between the drug concentrations and responses. Herein, we present an integrated PK/PD model of sunitinib and dopamine, which can quantitatively connect kinetics of both tumor burden and CSC frequency with the PK profiles.

Methods: Female Balb/c nude bearing MCF-7/Adr xenografts were treated with sunitinib, dopamine alone or in combination. PK profiles of sunitinib and its active metabolite SU12662 could be well fitted by a two-compartment model with first-order absorption. The response mediated by dopamine was incorporated via the on/off effect. Tumor volume and the CSC frequency in the tumor tissues were measured at different time points after drug administration. The final PK/PD model was established in according with the pharmacological process. Simulations were further conducted to achieve the optimum regimens.

Results: In the integrated PK/PD model, the tumor was divided into the CSC subpopulation and the differentiated tumor cell (DTC) subpopulation. A logistic growth model was introduced to describe the growth of CSCs, while the DTCs growth was analyzed by a nonlinear model. CSCs may transit to DTCs and vice versa, with different rate constants. Besides, we further found that sunitinib might increase the population of CSCs, as well as convert the proliferating DTCs to non-proliferating cells; while dopamine demonstrated inhibitive effect on the carrying capacity of CSCs, and promoted the differentiation process from CSCs to DTCs. According to the simulation results, low dose of sunitinib (qd) combined with dopamine (q3d) exhibited potent inhibitive effect on the tumor burden as well as the CSC frequency.

Conclusion: Critically, the present model may provide mechanistic insights into the quantitative pharmacology of sunitinib and dopamine, as well as the relationship between tumor burden and CSC frequency. Moreover, our model may offer reference for clinical practice, in which both of the tumor growth and CSC progression should be taken seriously and controlled precisely.

References:

[1] Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997;3:730-7.
[2] Donnenberg VS, Donnenberg AD. Multiple drug resistance in cancer revisited: The cancer stem cell hypothesis. J Clin Pharmacol. 2005;45:872-7.
[3] Ablett MP, Singh JK, Clarke RB. Stem cells in breast tumours: Are they ready for the clinic? Eur J Cancer. 2012;48:2104-16.
[4] Wang S, Mou Z, Ma Y, Li J, Li J, Ji X, et al. Dopamine enhances the response of sunitinib in the treatment of drug-resistant breast cancer: Involvement of eradicating cancer stem-like cells. Biochem Pharmacol. 2015;95(2): 98-109.

IV-56: *Sebastian Weber* Modeling Recurrent Safety Events in Drug Combinations using a Time-Varying Poisson Process

S. Weber, V. Stalbovskaya, C. Darstein, G. Heimann, P. Gopalakrishna, S. Roychoudhury
Novartis Pharma, Basel

Objectives: In phase I oncology studies a recommended phase II dose (RPIID) is declared at an early stage. With prolonged exposure a dose optimization of the RPIID becomes necessary. As an example, this work presents an evaluation of the RPIID based on recurrent safety adverse events (AEs) of a phase Ib study [1] of orally administered Ruxolitinib (RUX) and Panobinostat (PAN) for the treatment of patients with Myelofibrosis.

Methods: To understand the full safety profile the clinically relevant AEs are considered for analysis (e.g. thrombocytopenia CTCAE grade G3-4, anemia G3-4, diarrhoea G2-4 and asthenia G2-4). This analysis considers all occurrences of AEs in the dose escalation and the expansion phase. A one-compartment pharmacokinetic (PK) model with an effect compartment (EC) is used. The PK parameters are fixed using previous PK analyses. The recurrent AEs are modeled with a time-varying Poisson process [2]. We consider independent contributions to the intensity h(t) from the natural disease progression, h_0 (t), and each drug h_(1/2)(t). The events are considered as the result of the joint Poisson process such that h(t) is the sum over each component. As h_0(t) we use a Weibull form while we set h_(1/2)(t) proportional to the EC concentration. The model is fitted in a Bayesian framework using Stan [4] for each AE

Results: We evaluated the models using posterior predictive checks. These show that the AEs thrombocytopenia and anemia are not described satisfactory, while diarrhoea and asthenia AEs are well described. The baseline intensity had a large contribution (>50%). The key decision metrics calculated for regimens other than the RPIID with the model are (i) the predicted probability, P(≥1 AE), for at least one AE during 12 weeks and (ii) the relative reduction in cumulative hazard wrt. to the RPIID.
The limitations of the analysis are: (i) no individual PK data, (ii) no frailty term, (iii) assumption of linear PK and no DDI, (iv) more than 50% of the data at the RPIID.

Conclusions: The time-varying Poisson process with an *additive* intensity function was key to model independent contributions (in contrast to *proportional* approaches [3]).

The analysis established a dose-exposure-response relationship and enabled derivation of key decision metrics for alternative regimens wrt. to the RPIID. The key metrics derived from the model were communicated to the project team and were instrumental in the decision process.

References:
[1] Ribrag, V. et al., 55th ASH meeting, Dec. 7-10, 2013, https://ash.confex.com/ash/2013/webprogram/Paper56214.html
[2] Kalbfleisch, J.D. and Prentice, R.L., 2002, The Statistical Analysis of Failure Time Data, New Jersey, John Wiley & Sons
[3] Cox, Eugene H. et al., J. Pharmaco. and Biopharm., Dec 1999, Vol. 27, 6, pp 625-644
[4] Stan Development Team (2016). Stan: A C++ library for probability and sampling.

IV-57: *Janak Wedagedera* Investigating the Importance of Considering Inter-correlations of Cytochrome P450 Enzyme Abundances in Human Liver When Predicting Drug-Drug Interactions

Janak R. Wedagedera (1), Khaled Abduljalil (1), Theresa Cain (1), Masoud Jamei (1) and Amin Rostami-Hodjegan (1)(2)
(1) Simcyp (a Certara Company), Sheffield, United Kingdom (2) Manchester Pharmacy School, University of Manchester, Manchester, United Kingdom.

Objectives: We have previously compared the marginal distribution of 13 hepatic CYP450 enzymes with and without considering inter-correlations of absolute abundances using a PBPK modelling approach. The analyses revealed that CYP2D6 and CYP3A4 are moderately correlated enzymes in the liver. In present study we extend that work to assess the impact of these correlations when predicting drug-drug-interactions (DDI) using a model compound substrate of the above enzymes.

Methods: Using the Simcyp Simulator V15R1, simulations were performed for a drug not considering correlations between the CYP enzymes to obtain a control arm in a virtual population. The model compound is a substrate of both CYP2D6 and CYP3A4. Hepatic clearance values of this drug and its distributions are calculated assuming no other elimination route. In a second simulation, a DDI scenario was mimicked by reducing the hepatic clearance by 70% via inhibition of CYP2D6. The same scenario was repeated applying inter-correlation of CYP2D6 and CYP3A4. Finally, distributions of hepatic clearance values of the correlated and uncorrelated cases have been compared by calculating the Cramer statistic [2] for multivariate distributions.

Results: The population distribution of the hepatic clearance of the drug metabolised by CYP enzymes show significant differences between the mean, standard deviation and overall similarity of the correlated and uncorrelated samples assessed via Cramer statistic. When 70% of CYP2D6 mediated clearance is inhibited in both correlated and uncorrelated cases, the population mean in these two cases were significantly different.

Conclusions: The simulation results in this study indicate that incorporating the correlations between the abundance of the hepatic CYP450 enzymes can have an important impact on the prediction of hepatic clearance of drugs and the DDI level. It also highlights the importance of mechanistic incorporation of relevant covariates when developing population-based PBPK frameworks to generate more realistic virtual populations and conduct virtual clinical trials to assess drug safety and efficacy.

References:
[1] Brahim Achour, Matthew R. Russel, Jill Barber, and Amin Rostami-Hodjegan, Simultaneous Quantification of the Abundance of Several Cytochrome P450 and Uridine 59-Diphospho-Glucuronosyltransferase Enzymes in Human Liver Microsomes Using Multiplexed Targeted Proteomics, Drug Metab Dispos 42:500–510 (2014)
[2] Baringhaus, L. and Franz, C. (2004) On a new multivariate two-sample test, Journal of Multivariate Analysis, 88, p. 190-206

IV-58: *Gustaf Wellhagen* Carbohydrate intake contribution to HbA1c

Ahmad Fadli Mohamad Dahlan, Gustaf J. Wellhagen, Mats O. Karlsson, Maria C. Kjellsson
Department of Pharmaceutical Biosciences, Uppsala University

Objectives: To investigate the impact of different carbohydrate intakes to HbA1c for well-controlled and uncontrolled patients with type 2 diabetes (T2D) through model-predicted mean plasma glucose (MPG).

Methods: Data was simulated with the IGI model (1) mimicking different populations, well-controlled or uncontrolled T2D, by varying fasting plasma glucose (FPG) and fasting serum insulin (FSI). Glucose and insulin time-profiles were simulated following four different meal regimens: (I) Low carbohydrate intake, with three standard meals of 62.5 g glucose each, (II) Medium, with three standard meals and three snacks of 12.5 g, (III) High, with three standard meals and three large snacks of 25 g and (IV) decreased frequency, with the same carbohydrate intake as “Medium” but distributed on three large meals, 75 g each. MPG was calculated from the simulated profiles and used as input to the IGRH model (2) for simulation of HbA1c. The same individuals were tested with all dietary regimens and the difference in HbA1c was calculated relative to the Medium intake regimen.

Results: Predicted average HbA1c was 5.9% and 7.8% for well-controlled and uncontrolled patients following the Medium carbohydrate intake. For well-controlled patients, the mean difference relative to Medium was -0.07% (HbA1c units) for Low and +0.06% for High. For uncontrolled patients it was -0.04% for Low and +0.03% for High. Decreased frequency had a mean impact of around -0.03% for both test groups.

Conclusions: Our simulations show that carbohydrate intake has a small predicted impact on the HbA1c for uncontrolled patients (high FPG), while the impact is slightly larger for subjects with normal FPG (well-controlled T2D patients). Overall, the relatively small direct effect of carbohydrate intake on MPG and HbA1c as predicted by the combined IGI and IGRH models makes further investigation into indirect effects interesting to study. A primary indirect effect is the body weight changes associated with carbohydrate level intake and the impact this has on the glucose homeostasis.

References:
[1] Jauslin PM, Silber HE, Frey N, Gieschke R, Simonsson USH, Jorga K, et al. An Integrated Glucose-Insulin Model to Describe Oral Glucose Tolerance Test Data in Type 2 Diabetics. J Clin Pharmacol. 2007;47(10):1244–55.
[2] Lledó-García R, Mazer NA, Karlsson MO. A semi-mechanistic model of the relationship between average glucose and HbA1c in healthy and diabetic subjects. J Pharmacokinet Pharmacodyn. 2013 Apr;40(2):129–42.

IV-59: *Thomas Wendl* Computational Modelling of Personalized Hemodynamic Response to Valve Replacement Surgery in Heart Failure Patients

Denis Menshykau, Thomas Wendl, Katrin Coböken, and Thomas Eissing
Bayer Technology Services GmbH, Computational Systems Biology, Leverkusen, Germany

Objectives: We are developing a Cardiovascular (CV) Systems Pharmacology Platform, which integrates available knowledge of human CV physiology and information regarding drugs mode of action with the aim to predict whole-body hemodynamic response to pharmacological or other interventions.[1] On the basis of a publically funded and currently conducted clinical study on heart failure patients with aortic stenosis (SMART study[2]), we exemplify the capabilities of the developed platform with modelling patient response to aortic valve replacement surgery.

Methods: The CV Systems Pharmacology Platform includes a detailed description of the relevant physiology of the human CV system.[1,3] Based on obtained individual patient data before/after surgery, the CV model was individually adjusted to account for the mechanic properties of the malfunctioning/implanted aortic valve. These individualized models were parameterized to reproduce hemodynamic characteristics such as stroke volume, ejection fraction, heart rate, systolic and diastolic blood pressures in the corresponding patients with heart failure. The individualized CV models were used to identify changes in physiological parameters in patients before and after aortic valve surgery.

Results: Analysis of derived CV model parameters demonstrate that patients with aortic stenosis –in contrast to healthy individuals -have elevated peripheral resistance, reduced arterial compliance, altered end-diastolic pressure-volume relationship and increased end-systolic elastance. The pressure-volume loops inferred from patient data demonstrate that valve-replacement drastically reduces systolic pressure in the left ventricle. Furthermore, estimated arterial resistances of patients after surgery are comparable to those observed in healthy subjects and lower than before surgery. We finally discuss approaches to predict outcomes of valve replacement surgery based on clinical measurements before the surgery.

Conclusions: We developed a personalized computational model for the CV system of heart failure patients before and after a valve replacement surgery. Analysis of model parameters inferred from patient data provides additional information about the changes in the CV system induced by the surgery. Using the identified hemodynamic changes of the current patient population, the CV model enables predictions for future aortic valve stenosis patients. This, in turn, will facilitate an informed adjustment of the concomitant pharmacologic medication.

References:

[1] Coböken et al. Development of a Cardiovascular Systems Pharmacology Platform, PAGE-Meeting Poster 2015
[2] http://www.sys-med.de/en/demonstrators/smart/
[3] Eissing T. et al. A computational system biology software platform for the multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front. Physio. (2011)

IV-60: *Pawel Wiczling* A Bayesian approach for population pharmacokinetic modeling of dexmedetomidine during long-term infusion in critically ill pediatric patients.

Paweł Wiczling (1), Alicja Bartkowska-Śniatkowska (2), Oliwia Szerkus (1), Danuta Siluk (1), Jowita Rosada-Kurasińska (2), Justyna Warzybok (3), Agnieszka Borsuk (1), Roman Kaliszan (1), Edmund Grześkowiak (3), Agnieszka Bienert (3)

(1) Department of Biopharmaceutics and Pharmacokinetics, Medical University of Gdansk, Poland; (2) Department of Anaesthesiology and Intensive Therapy, Poznan University of Medical Sciences; (3) Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences

Objectives: The purpose of this study was to assess the pharmacokinetics of dexmedetomidine in the ICU settings during the long-term infusion and to compare it with the existing literature data using the Bayesian population modeling with literature-based informative priors.

Methods: 38 patients were included in the analysis with concentration measurements obtained at two occasions: first from 0 to 24 hr after infusion initiation and second from 0 to 8 hr after infusion end. The data analysis was conducted using WINBUGS software. The prior information on dexmedetomidine pharmacokinetics was elicited from the literature study pooling results from a relatively large group of children.

Results: A two compartment PK model with allometrically scaled parameters, maturation of clearance and t-student residual distribution on a log-scale was used to describe the data. The incorporation of time depended (different between the two occasions) PK parameters improved the model. It turned out that volume of distribution is 1.5-fold higher during the second occasion. There was also an evidence of increased (1.3-fold) clearance for the second occasion with posterior probability of 62%.

Conclusion: A population PK model of dexmedetomidine was developed. The application of Bayesian modeling with informative priors allowed elucidation of time-dependent changes in PK parameters during the long-term infusion using poorly informative data.

IV-61: *Rixt Wijma* Population pharmacokinetics of meropenem during intermittent and continuous infusion in healthy volunteers

Rixt A. Wijma
Erasmus University Medical Center

Objectives: Meropenem is a broad-spectrum antibacterial agent that has been used for decades. In an era of increasing emergence of drug resistance and lack of new antibiotics, old off-patent antibiotics are increasingly being prescribed to patients. However, many of these were developed in an age before the advent of a structured process for drug assessment and approval. As part of a large, European project, this study was conducted to describe the population pharmacokinetics of intravenous meropenem to optimize plasma levels related to MICs.

Methods: Eight healthy volunteers received meropenem on 2 separate occasions either intermittently (3 doses, 10 mg/kg every 6 hours, infusion time 25 minutes) or by continuous administration (30 mg/kg meropenem over 18h with a loading dose of 0.2 mg/kg). Venous blood samples during the intermittent regime were taken before the third dose and at: 10, 20, 30, 40, 50, 60 min and 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 h after the start of the third infusion. Blood samples during the continuous regime were taken before the loading dose and at: 10, 20, 30, 40, 50, 60 min and 1.5, 2, 4, 8, 12, 14, 16, 18, 19, 20, 22, 24 and 26 h after the start of the infusion. . The data were analysed with nonlinear mixed effect modelling (NONMEM, version 7.2.0) [1]. One-, two- and three-compartments were evaluated in combination with different covariates. Model selection criteria were decrease in objective function, diagnostic plots and visual predictive checks.

Results: A two-compartment model fitted the data best with volume of distribution and clearance as relevant covariates. Clearance and volume of the central compartment were 19.3 ± 0.6 L/h and 13.1 ± 0.8 L, respectively. Forward inclusion and backward elimination was used to test significant improvement of the model by the covariates. Neither age, weight, nor creatinine clearance was found to be significant. No between occasions variability was found.

Conclusions: The pharmacokinetics of meropenem is best described by a two-compartment model with no covariates. Our results show that the pharmacokinetics of meropenem are stable in this population. This is not comparable with earlier research were body weight and creatinine clearance were found to be significant covariates [2,3]. This can be explained by the fact that these studies were conducted in patients with different pharmacokinetic properties.

References:

[1] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.
[2] Chonghua Li, Joseph L. Kuti, Charles H. Nightingale et al. Population Pharmacokinetic Analysis and Dosing Regimen Optimization of Meropenem in Adult Patients. Journal of Clinical Pharmacology, 2006; 46:1171-1178.
[3] Amelia Ramon-Lopez, Jane M. Allen, Alison H. Thomson, et al. Dosing regimen of meropenem for adults with severe burns: a population pharmacokinetic study with Monte Carlo simulations. J Antimicrob Chemother 2015; 70: 882–890.

IV-62: *Jayson Wilbur* Zika microcephaly cutoffs revisited: A study of Non-parametric methods in fetal growth

Jayson D. Wilbur (1,6), Eric Ohuma (2,6), Luo Xiao (3,6), Samer Mouksassi (4,6) and Ryan Hafen (5,6)
: (1) Metrum Research Group, Tariffville CT, (2) University of Oxford, Oxford UK, (3) North Carolina State University, Raleigh NC, (4) Certara, Montreal QC, (5) Hafen Consulting, Seattle WA, (6) Representing the Healthy Birth, Growth and Development knowledge integration (HBGDki) community, Sponsored by the Bill & Melinda Gates Foundation, Healthy birth, growth and development initiative

Objectives: An observed increase in the number of cases of microcephaly in Brazil has been associated with exposure to the Zika virus. In response, a number of organizations have published screening thresholds for microcephaly in terms of measured newborn head circumference [1]. This work evaluates these criteria based on modeling of data on longitudinal fetal growth trajectories and newborn size.

Methods: Functional Principal Components Analysis (fPCA) was employed to model head circumference growth trajectories using non-parametric functions to characterize both the mean trajectory and subject-level random effects.

Results: As expected, microcephaly thresholds that do not account for gestational age ignore an important source of biological variation. However, factors associated with maternal health also contributed to population and subject level deviations from international standards, which do account for gestational age [2].

Conclusions: Establishing fixed cutoffs for microcephaly in terms of newborn head circumference size ignores important sources of variation which can be accounted for using a model-based approach.

References:

[1] Victora, Cesar Gomes, et al. "Microcephaly in Brazil: how to interpret reported numbers?" *Lancet* (London, England) 387.10019 (2016): 621-624.
[2] Villar, José, et al. "International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project." The Lancet 384.9946 (2014): 857-868.

IV-63: *Julia Winkler* Population pharmacokinetics of lacosamide to support intravenous dose adaptation in children with epilepsy

Julia Winkler (1), Rik Schoemaker (2), Armel Stockis (3)
(1) SGS Exprimo, Mechelen, Belgium, (2) Occams, Amstelveen, The Netherlands, (3) UCB Pharma, Braine l'Alleud, Belgium

Objectives: To predict the intravenous (IV) PK profile of lacosamide (LCM) in children, by combining the healthy adult IV and oral PK characteristics from two bioavailability studies with the pediatric oral PK characteristics obtained from a recently developed population PK model, to simulate different dosing regimens of IV infusions of LCM in pediatric subjects with epilepsy, and to propose dose adaption rules.

Methods: A population PK model was developed for LCM using a combined dataset of healthy adult subjects with IV and oral dosing and pediatric subjects with epilepsy with oral dosing (using NONMEM v.7.2.0 with FOCEI). A structural model with zero and first order absorption after oral administration, two compartment distribution, and first order elimination described the data well. Plasma clearance was modelled using allometric scaling on body weight with a fixed theoretical allometric exponent, and volume of distribution with a freely estimated allometric exponent. Residual error was modeled using separate proportional error terms for the adult and pediatric population. In addition, co-administration of enzyme-inducing drugs was included as a covariate on clearance.

The final model was used to predict different LCM IV dosing regimens with varying duration (15-60 min) in pediatric subjects with epilepsy and to propose dose adaption rules.

Results: LCM plasma concentration-time data were available from 43 intensely sampled healthy adult subjects (n=1735), and from 72 sparsely sampled and 7 intensely sampled children (body weight 6–76 kg) (n=402), with 9, 26, 23, and 21 patients in age groups 0 to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years, respectively.

Median steady state peak plasma concentrations (Cmax) at the end of a 15-min IV infusion were predicted to be 9-21% higher compared to median Cmax values after oral administration; this decreased to 2-10% after a 60-min IV infusion. Exposure was fairly similar between both routes of administration and independent of infusion duration supporting the interchangeability of oral and IV dosing approved in adults.

Conclusions: The model adequately described LCM plasma concentrations in healthy adults and children with epilepsy. Model-based PK predictions suggest that there is no need to adapt the recommendations regarding IV infusion durations in children compared to adults using weight-based dosing with or without loading doses aiming to reach exposures in the same range as in adults.

IV-64: *Jan-Georg Wojtyniak* A cancer cell cycle model to predict effects of combination therapy and different dosing schedules on cell cycle, tumor growth and therapy outcome

Jan-Georg Wojtyniak (1), Johanna Liebl (2) and Thorsten Lehr (1)
(1) Clinical Pharmacy, Saarland University, Saarbruecken, Germany, (2) Department of Pharmacy - Center for Drug Research, University of Munich, Munich, Germany

Objectives: Despite intensive research in the field of cancer pathogenesis, today's modern chemotherapy still relies on empirical values rather than a rational design [1]. Thus, the development of a novel mathematical semi-mechanistic cancer cell cycle model that allows the prediction of combination chemotherapy effects and different dosing schedules on cell cycle and tumor growth, was aspired.

Methods: The model was based on FACS *in vitro* and xenograft *in vivo* data by Ehrlich et al. [2], describing single and combination effects of the chemotherapeutics Irinotecan and Roscovitin on HUH7 and HUH7 CDK5 shRNA cells. Model development was done using NONMEM V7.3 [3] by testing several cell cycle phase compartments and transit compartments [4]. The quality of different models was assessed based on common statistical and graphical diagnostics. Also placebo, single compound treatment and Irinotecan in combination with Roscovitin treatment data were implemented in a stepwise procedure. The final model was evaluated by predicting prior excluded data. Comparison of simulated treatment regimens was realized through estimation of the tumor growth inhibition (TGI).

Results: The final model consisted of three main compartments corresponding to G1, S and G2/M phases, respectively. All in all seven transit compartments were implemented. Two of them concerned transit from G1 to S phase, while the remaining five were required to describe S to G2/M transit. For all treatments static effect parameters could be estimated. In *vivo* tumor growth under Irinotecan treatment was successfully predicted by only using the data of cycle distribution under treatment and placebo tumor growth. Combination therapy effects on tumor growth could be predicted using placebo and single compound effects. Comparing the simulated TGIs of treatment combinations revealed synergistic effects.

Conclusions: A novel mathematical semi-mechanistic cancer cell cycle model was developed and successfully used to predict single treatments as well as combination treatment effects of both common and new dosing schedules and drug combinations. This approach demonstrates that the model holds the capability to act as a pioneering tool for a rationalized and data based decision making in tumor therapy by providing striking pre-evaluations of newly developed chemotherapy protocols.

References:

[1] Pinto, A. C., Moreira, J. N. and Simões, S. Combination Chemotherapy in Cancer : Principles , Evaluation and Drug Delivery Strategies. Curr. Cancer Treat. 695–714.
[2] Ehrlich, S. M. et al. Targeting cyclin dependent kinase 5 in hepatocellular carcinoma--A novel therapeutic approach. J. Hepatol. 63, 102–13.
[3] Beal, S. L., Sheiner, L. B., Boeckmann, A. J., and Bauer, R. J. (eds) NONMEM 7.3.0 Users Guides. (1989–2013). ICON Development Solutions, Hanover, MD.
[4] Savic, R. M., Jonker, D. M., Kerbusch, T. and Karlsson, M. O. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J.Pharmacokinet. Pharmacodyn. 34, 711–26.

IV-65: *Dan Wright* A population pharmacokinetic model for 51Cr EDTA, an isotopic biomarker for renal function: impact on carboplatin dosing.

Daniel F.B. Wright
School of Pharmacy, University of Otago, Dunedin, New Zealand

Objectives:

1. To develop and test a population pharmacokinetic (PK) model for ^{51}Cr EDTA disposition.
2. To compare the model predictions for renal function (glomerular filtration rate, GFR) to those estimated by conventional methods.
3. To determine if differences in predicted GFR could change dosing decisions in the clinic using carboplatin as a test case.

Methods: Data from 40 individuals who received 2 mL (~3.7 MBq/mL) of ^{51}Cr EDTA were available for analysis [1]. Four plasma concentrations were measured at approximately 2, 4, 6 and 24 hours after the dose. A population analysis was conducted using NONMEM® v.7.2. Model stability was assessed using a simulation-estimation (sim-est) procedure. Predictions of GFR from the PK model were compared to conventional methods for estimating renal function using mean prediction error (MPE) and root mean square error (RMSE). Creatinine clearance (CLcr) estimated using 24 urine collection was used as a control. Carboplatin dosing was simulated using the Calvert formula [2] for two hypothetical patients.

Results: A total of 159 ^{51}Cr EDTA plasma concentrations from 40 patients were analysed. A two compartment PK model with first-order elimination best fit the data. Significant covariates included creatinine clearance on ^{51}Cr EDTA clearance and weight on central volume. The control, CLcr estimated using a 24-hour urine collection method, provided the closest predictions to the model and was unbiased. However, commonly used eGFR equations (i.e. Cockcroft Gault, MDRD and CKD-Epi) led to negatively biased estimates relative to the model (MPE -19.5 mL/min/1.73m^2, -20.6 mL/min/1.73m^2 and -16.9 mL/min/1.73m^2, respectively). The commonly used 'slope-intercept' method for estimating isotopic (^{51}CR EDTA) GFR led to positively biased estimates compared to the model (MPE 15.1 mL/min/1.73m2). Carboplatin doses for a healthy young male representing a typical testicular cancer patient with normal renal function were over-predicted by 116 mg (13%) when GFR was determined using the slope-intercept method versus the model and under-predicted by 134mg (15%), 222mg (25%) and 156mg (18%) when using the eGFR equations, Cockcroft Gault, MDRD and CKD-Epi, respectively.

Conclusions: A population pharmacokinetic model for the disposition of ^{51}Cr EDTA was developed and evaluated. The model provided unbiased estimates of renal function. The biased renal function estimates provided by both eGFR equations and the conventional method for estimating isotopic (^{51}CR EDTA) GFR would lead to clinically important differences in carboplatin doses.

References:

[1] Putt TL *et al*. (2014) *Eur J Clin Pharmacol* 70:1221-6
[2] Calvert AH *et al*. (1989) *J Clin Oncol* 7:1748-56

IV-66: *Li Xia* Population pharmacokinetics of multiple oral doses of alcohol in humans using blood and breath measures

Xia Li*, Max Taubert, Yingying Tian, Malaz Gazzaz, Uwe Fuhr*
Department of Pharmacology, Clinical Pharmacology, Cologne University Hospital, Cologne, Germany

Objectives: We conducted a cocktail drug-drug interaction study to evaluate the effect of acute ethanol consumption on the most important drug-metabolising cytochrome P450 enzymes, NAT2 and P-glycoprotein. The aim of the present evaluation was to accurately describe internal ethanol exposure in this study. Primary metabolism of ethanol occurs essentially in the liver and is mainly mediated by a group of alcohol dehydrogenase isoforms, but to a minor extent also by other enzymes including cytochrome P450 CYP2E1. The availability of NAD+ limits ethanol oxidation, causing saturating kinetics.

Methods: Data were obtained from an open-labeled, single-center, two-way, cross-over study in 16 healthy volunteers (8 males, 8 females), aged from 20 to 52 years old, with a body weight (BW) from 54.5 to 97.0 kg. During test period, the initial ethanol doses (ml) were 1.925 × BW and 1.65 × BW for male and female,respectively. After 2 hours, the cocktail consisting of omeprazole, tolbutamide, caffeine, dextromethorphan and digoxin was given. Thereafter, additional doses of ethanol were given five times at 4 hours intervals: males, 0.77 × body weight (kg); female, 0.66 × body weight (kg). During the reference period, the cocktail was administered without ethanol. Blood ethanol concentrations C (measured at 9 time points by gas chromatography) and breath concentrations CB (measured at 6 time points, Draeger breath analyzer Alcotest 7410 plus, Drägerwerk AG, Lübeck, Germany) were collected. CB was assumed to be related to C as described by equation 1: C= M × CB. Data analysis was performed by the population pharmacokinetic approach using non-linear mixed effects modeling (NONMEM 7.2.0).

Results: A one-compartment model with a single Michaelis-Menten elimination pathway was not only suitable as the basic model,but also was clearly better than linear or exponential concentration decline (ΔOFV, -9.291). The value of Km could not be estimated and thus was fixed as 0.0821 g/L according to the literature [1]. As for covariates, volume of distribution V had a significant relationship with subject body weight (ΔOFV, -152.53), and sex had a small albeit significant effect on maximal elimination capacity VM (ΔOFV, -19.285). Covariate model:

Vmax = θ[VM] *(1+ (SEX-1)* θ[Sex on Vmax] (0 = Male; 1 = Female); V= θ[V] * (Weight/71.6) ^ θ [Weight on V]

The mean and relative standard error of the parameter estimates derived from the study were Vmax 7.01 g/h (3 %), V 31.7 L(3 %), Ka 1.4 h^{-1} (7 %), M 1850 (2 %), θ [Weight on V] 1.44 (9 %), θ [Sex on Vmax -0.39 (18 %). Although the data were obtained from blood and from breath ethanol concentration, they were integrated well with the introduction of equation 1.

Conclusions: Despite the involvement of multiple enzymes, a simple model was suitable to describe internal ethanol exposure. Results are in accordance with published data.

References:
[1] Wilkinson PK, Sedman AJ, Sakmar E, Earhart RH, Weldler DJ, Wagner JG. Blood ethanol concentrations during and following constantrate intravenous infusion of alcohol. Clin Pharmacol Therap 19, 1975. 213-

223.

IV-67: *Gulbeyaz Yildiz Turkyilmaz* Investigating the ability of population PK models to characterize secondary exposure parameters

Gülbeyaz Yildiz Türkyilmaz (1,2,3), Siv Jönsson (1), Mats O Karlsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden, (2) Center For Drug Research & Development And Pharmacokinetic Applications (ARGEFAR), Ege University, TURKEY, (3) Department of Pharmaceutical Technology, Faculty of Pharmacy, Ege University, Turkey

Objectives: To explore how well Pop PK models characterize the NCA parameters Cmax and AUC(0-t) in rich data setting and the influence of the absorption delay model choice.

Methods: The investigation was performed based on PopPK models for five real drug data sets with rich sampling [1-5]. Alternative models, with respect to the delay part of absorption, were evaluated for each data set (no delay, lagtime or transit compartment), using NONMEM 7.3 [6]. Simulations were conducted using *nca* in Perl-Speaks-NONMEM (PsN) [7, http://psn.sourceforge.net/]. The *ncappc* package [8] generated population and individual diagnostics were inspected and summarized across the different models and data sets. For each model, across drugs and NCA parameters, 30 population level metrics were generated; the observed population mean (Pop_Mean) compared with the 95% nonparametric prediction interval (npi), and the population mean and SD (including 95% CIs) of the NPDEs compared with the expected values (i.e. mean 0, SD 1). The individual level metrics generated across individuals, drugs and NCA parameters were the deviation of mean individual simulated NCA parameter from corresponding individual observed parameter (PPC_Outlier, outlier defined as deviation outside the 95% npi) and the NPDE of each NCA parameter (NPDE_Outlier, outlier defined as NPDE outside +/- 2 SD from mean).

Results: The transit compartment model resulted in the best fit for all drugs based on the OFV (reduction in OFV versus no delay ranged from 237 to 662). The transit model performed well for Cmax and AUC(0-t) for 5 and 4 data sets, respectively, for Pop_Mean (95% npi covered observed mean), and for 2 out of 5 drugs for both NPDE_Mean and NPDE_SD. Thus, 8 out of 30 metrics were outside the 95% PIs. For the lagtime and no delay models, the corresponding values were 10/30 and 17/30. For Cmax, across all models, the percentage identified individual subject outliers were in agreement with expectations; PPC_Outlier 3.6–6.3% vs expected 5%, and NPDE_Outlier 3.6-5.7% vs expected 4.5%. Corresponding PPC_Outlier and NPDE_Outlier values for AUC(0-t) were 2.7%-3.9%, and 2.7-3.3%, respectively.

Conclusion: Overall, the PopPK models described the mean and interindividual variability in the secondary metrics Cmax and AUC(0-t) reasonably well. The evaluation of NCA metrics was made easy by PsN and the *ncappc* package and choice of absorption delay model affected the quality of both Cmax and AUC(0-t) simulations.

References:
[1] Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34(5):711-26.
[2] Bååthe S, Hamrén B, Karlsson MO, Wollbratt M, Grind M, Eriksson UG. Population pharmacokinetic of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran, in atrial fibrillation patients receiving long-term anticoagulation therapy. Clin Pharmacokinet. 2006;45(8):803-19.
[3] Karlsson MO, Jonsson EN, Wiltse CG, Wade JR. Assumption testing in population pharmacokinetic models: Illustrated with an analysis of Moxonidine data from congestive heart failure patients. J Pharmacokinet Biopharm. 1998;26(2):207-46.

[4] Jönsson S, Davidse A, Wilkins J, van der Walt JS, Simonsson USH, Karlsson MO, Smith P, Mcllleron H. Population pharmacokinetic of ethambutol in south African Tuberculosis patients. Antimicrob Agents Chemother. 2011;55(9):4230-7.
[5] Karlsson MO, Sheiner LB. The importance of modelling interoccasion variability in population pharmacokinetic analyses. J Pharmacokinet Biopharm. 1993;21(6):735-50.
[6] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ. NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA
[7] Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol. 2013;2:e50.
[8] Acharya C, Hooker AC, Yildiz Türkyilmaz G, Jönsson S, Karlsson MO. A diagnostic tool for population models using non-compartmental analysis: The *ncappc* package for R. Computer Methods and Programs in Biomedicine (accepted for publication 2015)

IV-68: *Younghoon Yoo* Pharmacokinetic Model for subconjunctival injection of bevacizumab in Rabbits.

Younghoon Yoo (1), Hwi-yeol Yun (1), Byungjeong Song (1), Hyun-moon Back (1), Siyoung Hwang (1), Eben Jung (1), Kwang-il Kwon (1) and JaeWoo Kim(2)
(1) College of Pharmacy, Chungnam National University, Daejeon, Korea, (2) Clinical Trials Center, Chungnam National University Hospital, Daejeon, Korea

Objectives: Recent studies have shown that intravitreal or intracameral injection of bevacizumab, a full length anti-VEGF antibody, may be a useful adjunct in the treatment of neovascular glaucoma. One way of delivering macromolecules is subconjunctival injection. But in each eye, the concentration of bevacizumab has different conditions. Pharmacokinetic model for subconjunctival administration of bevacizumab had not been developed yet. In this study, we developed pharmacokinetic model for subconjunctival administration of bevacizumab and investigated reason of different concentration.

Methods: The right eye of 33 rabbits was injected with 2.5 mg of subconjunctival bevacizumab. Three rabbits were sacrificed at each of the following time points: 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 120, 168 h after the injection. Bevacizumab concentrations were measured in aqueous fluid of injected and un-injected eyes and serum.[1] Pharmacokinetic model of bevacizumab was developed by NONMEM(ver. 7.3). The model parameters was estimated using First-order conditional estimation and evaluated using goodness of fit (GOF) and visual predict check (VPC, n=1000).

Results: Bevacizumab was first detected in the aqueous humor of the injected eye at 12 h after the subconjunctival injection. Bevacizumab was also detected in the serum and aqueous humor of the un-injected contralateral eye. The concentration in the aqueous humor of the injected eye was lower than in the serum and higher than in the aqueous humor of the un-injected contralateral eye at all time points. Subconjunctival injection model was developed with six-compartments including subconjunctival space and each vitreous humor compartments. Serum volume of distribution(V_C), absorption rate constants(k_a), clearance(CL) and aqueous humor volume of distribution(V_A) of this model is 0.347mL, 0.698hr^{-1}, 286mL/hr and 3.62mL, respectively. As a result of GOF and VPC, our subconjunctival injection model was robust and parameter values were reliable.

Conclusions: We demonstrated that bevacizumab can be delivered into anterior chamber by single subconjunctival injection. Pharmacokinetic model for subconjunctival injection of bevacizumab was successfully developed and evaluated. The model was appropriate to predict the plasma and aqueous humor of each eye concentration of bevacizumab in rabbits and may be useful to develop human model with neovascular glaucoma in further study.

References:
[1] kim MJ, Han ES, Kim JW, Kim TW. Aqueous Humor Concentration of Bevacizumab After Subconjunctival Injection in Rabbit. Journal of ocular pharmacology and therapeutics(2010)26(1): 49-54

IV-69: *Seonghae Yoon* Population pharmacokinetic analysis of oxcarbazepine in patients with epilepsy

Seonghae Yoon (1) Su-jin Rhee (1), Tae-Joon Kim (2), Sang Kun Lee (2), Kon Chu (2) and In-jin Jang (1)
(1) Department of Clinical Pharamcology and Therapeutics, Seoul National University Hospital and College of Medicine, South Korea, (2) Department of Neurology, Laboratory of Neurotherapeutics, Comprehensive Epilepsy Center, Biomedical Research Institute, Seoul National University Hospital and College of Medicine, South Korea

Objectives: Oxcarbazpine is a widely used anticonvulsant drug to treat partial seizure as monotherapy or adjunctive therapy. The mono-hydroxylated derivative (MHD) is the main metabolite which is responsible for most of the anticonvulsant activity. The objectives of this study to develop a PK model of oxcarbazepine and to analyse the relationship between trough concentrations of the drug and occurrence of adverse event (AE) or seizure.

Methods: To develop a PK model of oxcarbazepine, the data from two studies were used; the data of 447 patients who had been enrolled in from Epilepsy Registry Cohort of Seoul National University Hospital since Feb 2011 and the data of PK study involving 40 patients evaluating oral loading of oxcarbazepine [1]. Plasma concentrations of MHD were analysed using nonlinear mixed-effect modelling in NONMEM (ver 7.3). The first-order conditional estimation (FOCE) with interaction method was used to fit the plasma concentration-time data. The trough concentrations (C_{min}) of each patients were calculated using the final PK model. The relation between trough concentrations and occurrence of AE or seizure were analysed using Students' t-test.

Results: A one-compartment model with first-order absorption, and a proportional error model describes oxcarbazepine PK adequately. The body weight was significant covariate for the clearance and the volume of distribution of the drug and the use of concomitant drugs including carbamazepine, phenytoin, and phenobarbital which are known to be enzyme-inducers increased the clearance 1.38-fold. The daily dose per body weight (DDPBW) and the C_{min} of the drug were slightly higher in the patients group with AEs (mean ± SD; DDPBW 17.1 ± 5.0 mg/kg, C_{min} 13.4 ± 7.8 ng/mL) or with seizure episodes more than once (16.4 ± 4.3 mg/kg, 13.9 ± 7.6 ng/mL) compared to the non-AE group (14.5 ± 4.6 mg/kg, 12.4 ± 6.8 ng/mL) or non-seizure group (15.4 ± 4.9 mg/kg, 12.7 ± 7.2 ng/mL) but the differences were not statistically significant.

Conclusion: The population PK model developed in this study adequately described oxcarbazepine PK in patients with epilepsy. The covariates selected in this study including body weight and the use of concomitant drug are expected to be used to choose appropriate dosage regimen in the patients.

References:
[1] Kim DW1, Gu N, Jang IJ, Chu K, Yu KS, Cho JY, Yoon SH, Kim HS, Oh J, Lee SK. Efficacy, tolerability, and pharmacokinetics of oxcarbazepine oral loading in patients with epilepsy. Epilepsia, 53(1):e9–e12, 2012

IV-70: *Huixin Yu* Development of a pharmacokinetic model for pazopanib – a tyrosine kinase inhibitor used for the treatment of solid tumours

Huixin Yu (1), Nielka P. van Erp (2), Sander Bins (3), Ron H. J. Mathijssen (3), Jan H. M. Schellens (4, 5, 6), Jos H. Beijnen (1, 5, 6), Neeltje Steeghs (4,5), Alwin D. R. Huitema (1,5)
(1) Department of Pharmacy & Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek and MC Slotervaart, Amsterdam, NL; (2) Department of Clinical Pharmacy, Radboud University Medical Center, Nijmegen, NL; (3) Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, NL; (4) Department of Medical Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, NL; (5) Department of Clinical Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, NL; (6) Department of Pharmaceutical Sciences, Utrecht University, Utrecht, NL.

Objectives: Pazopanib is a tyrosine kinase inhibitor that has been approved for the treatment of renal cell carcinoma and soft tissue sarcoma at an oral dose of 800 mg daily. Pazopanib is insoluble at neutral pH in water and, consequently, has a complex absorption profile. The primary aim of this study was to develop a pharmacokinetic (PK) model for pazopanib. The secondary aims were to understand the absorption profile, dose-concentration relationship, inter- and intra- patient variability, and change over time in concentrations of pazopanib.

Methods: This analysis included the PK data of pazopanib collected in 96 patients from three clinical studies [1–3]. Various numbers of compartments and different absorption models were explored. The relationship between relative bioavailability (*rF*) and dose was investigated. It was also explored whether a decrease over time in the concentrations of pazopanib could be identified. In one of the three clinical studies [3], the inducing effects of ifosfamide on pazopanib clearance was modelled with fixed parameter estimates based on previously published enzyme turn-over model of ifosfamide auto-induction [4]. In addition, inter- and intra- patient variability on *rF* was estimated.

Results: A two-compartment model best described the PK of pazopanib. The absorption phase of pazopanib was best modelled by two first-order processes: firstly, 36% (relative standard error (RSE) 34%) of pazopanib was absorbed at a relatively fast rate (0.4 h^{-1} (RSE 31%)); after a lag time of 1 hour (RSE 29%), the remaining part of the pazopanib dose was absorbed at a slower rate (0.1 h^{-1} (RSE 28%)). The *rF* at 200 mg dose level was fixed to 1; with increasing dose *rF* was found to reduce by an Emax manner with Emax fixed to 1 and the dose at half of maximum effect estimated as 480 mg (RSE 23%). The *rF* of pazopanib was found to decrease with a maximum magnitude of 50% (RSE 27%) and an exponential-decay constant of 0.15 day^{-1} (RSE 43%). The inter- and intra -patient variability on *rF* were estimated as 35.6% and 74.5%, respectively. The residual error model was a combined model estimated with proportional and additive errors.

Conclusions: A PK model for pazopanib was successfully developed. This model studied and illustrated the complex absorption process, the non-linear dose-concentration relationship, high inter- and intra- patient variability, and the exponential-decay of concentration of pazopanib in time.

References:
[1] de Wit D, van Erp NP, den Hartigh J, et al. Therapeutic Drug Monitoring to individualize the dosing of pazopanib: a pharmacokinetic feasibility study. Ther Drug Monit. 2014;37:331–8.
[2] Hamberg P, Mathijssen RHJ, de Bruijn P, et al. Impact of pazopanib on docetaxel exposure: results of a phase I combination study with two different docetaxel schedules. Cancer Chemother Pharmacol.

2014;75:365–71.
[3] Hamberg P, Boers-Sonderen MJ, van der Graaf WTA, et al. Pazopanib exposure decreases as a result of an ifosfamide-dependent drug-drug interaction: results of a phase I study. Br J Cancer. 2014;110:888–93.
[4] Kerbusch T, Huitema ADR, Ouwerkerk J, et al. Evaluation of the autoinduction of ifosfamide metabolism by a population pharmacokinetic approach using NONMEM. Br J Clin Pharmacol. 2000;49:555–61.

IV-71: *Jurij Zdovc* Pharmacokinetics of vancomycin in intensive-care patients

Jurij Zdovc, Carla Ferreira Santos, Nuno Silva, José Augusto Guimarães Morais, Paulo Paixão
Faculty of Pharmacy, Universidade de Lisboa

Objectives: Vancomycin has been used and still is being used as an effective antibiotic. Nevertheless, there is still a need to gather data and improve approaches to improve the correlation between a patient's pathophysiologic characteristics and vancomycin pharmacokinetics. Since it is often used as a »drug of last resort» against Gram-positive bacteria, individually adjusted treatment is of utmost importance to achieve an efficient treatment. This is a critical need because of the increasing resistance of bacteria in the past years. The aim of the study was to analyze and clarify the influence of personal characteristics on the pharmacokinetics of vancomycin and to provide a population pharmacokinetic model through which one could adjust and optimize dosing in an individual patient.

Methods: This was a retrospective study of concentration-versus-time data for vancomycin in plasma on a population of 33 critically ill patients from the Hospital Center Tondela – Viseu. The data from the patients' medical histories was analyzed by a population pharmacokinetic approach (nonlinear mixed effects modeling) using Adapt 5. The significant covariates were detected by means of an ANOVA test and then analyzed in relation to the base model. We used »forward selection» process to construct and choose the best fitting model. The expectation-maximization algorithm was used to adjust the data to the model and obtain the maximum likelihood of the parameters. A validation of the model with the lowest Bayesian Information Criterion was performed using bootstrapping with substitution (n=50).

Results: The best pharmacokinetic model consisted of a one-compartment linear model with additive residual unknown variability and total body weight and renal function as covariates describing a between-subject variability (BSV). The volume of distribution was 64.9 L with a BSV of 66.6% and was proportionally associated to the total body weight (78.8 ± 17.0 kg). The clearance of vancomycin was 4.02 L/h with a BSV of 30.6% and was associated with creatinine clearance as a marker of renal function (128 ± 50.5 ml/min; Cockcroft-Gault equation). Residual unknown variability was 2.96 mg/L. The model was shown to be robust, since no 95% confidence intervals included zero and the results were within that interval.

Conclusions: The study showed that the total body weight and renal function play an important role in the individualized therapy with vancomycin and that the dosing regime should be adjusted accordingly in order to achieve an optimized treatment.

References:
[1]Matzke G., Zhanel G., Guay D. (1986). Clinical pharmacokinetics of vancomycin. *Clinical Pharmacokinetics,* 11, 257-282.
[2]Shorr A. (2007). Epidemiology of staphylococcal resistance. *Clinical Infectious Diseases*, 45 (3), 171-176.
[3]Johnson A., Henwood C., Mushtaq S., James D., Warner M., Livermore D. (2003). Susceptibility of Gram-positive bacteria from ICU patients in UK hospitals to antimicrobial agents. *The Journal of Hospital Infection*, 54(3), 179-187.
[4]Streit J., Jones R., Sader H., Fritsche T. (2004). Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). *International Journal of Antimicrobial Agents,* 24(2), 111-118.
[5]Jones M., Draghi D., Thornsberry C., Karlowsky J., Sahm D., Wenzel R. (2004). Emerging resistance among bacterial pathogens in the intensive care unit – a European and North American surveillance study (2000–

2002). *Annals of Clinical Microbiology and Antimicrobials*, 3(14).
[6]Rybak M., Lomaestro B., Rotschafer J., Moellering R., Craig W., Billeter M., Dalovisio J., Levine D. (2009). Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clinical Infectious Diseases*, 49(3), 325–327.
[7]Drugbank.ca, Vancomycin, (2005). *Drug bank*. [online] Available at: http://www.drugbank.ca/drugs/DB00512 [Accessed June 2015]
[8]Ette E., Williams P. (2004) Population Pharmacokinetics I: Background, Concepts, and Models. *Annals of Pharmacotherapy,* 38(10), 1702-1706
[9]Ette E., Williams P. (2004) Population Pharmacokinetics II: estimation methods. *Annals of Pharmacotherapy,* 38(11), 1907-1915
[10]Revilla N., Martín-Suárez A., Perez M., González F., Gatta M. (2010) Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/ pharmacodynamic simulation. *British Journal of Clinical Pharmacology,*70(2), 201-212
[11]Roberts J., Taccone F., Udy A., Vincent J., Jacobs F., Lipman J. (2011) Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens. *Antimicrobial agents and chemotherapy*, 55(6), 2704-2709
[12]Sopotnik F. (2012) Populacijska farmakokineticno-farmakodinamicna analiza za ocenjevanje primernosti odmerjanja vankomicina pri kriticno bolnih. Diplomska naloga, Fakulteta za farmacijo, Univerza v Ljubljani

IV-72: *Fan Zhang* Population pharmacokinetic modeling of lamotrigine in Chinese subjects

Fan Zhang (1), Peiming Ma (1), Huafang Li (2), Chao Chen (3)
(1) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, China; (2) Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China; (3) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, UK

Objectives: The apparent bimodal distribution of lamotrigine clearance, previously described by a mixture model, has led to regulatory acceptance of bioequivalence (BE) between two formulations despite a BE study that missed the acceptance criterion. The objective of the present work was to describe lamotrigine population pharmacokinetics (PK) in Chinese population using data from multiple studies, applying a mixture model as appropriate to investigate clearance (CL) distribution characteristics in Chinese population.

Methods: Four GSK funded PK studies were conducted in healthy Chinese subjects (196 males and 6 female) in the mainland and Hong Kong for two oral formulations, lamotrigine dispersible/chewable (DC) and compressed tablets, at 25 and 100 mg doses. PK models were fitted to plasma concentrations using a non-linear mixed-effect model implemented in NONMEM V7.3.0 and Monolix V4.33. Effects of body weight, age, sex, dose, formulation, and region on PK parameters were evaluated. A mixture model with two subpopulations in clearance (CL) was tested on the dataset. Parameter estimates from the final runs in NONMEM and Monolix were compared.

Results: A two-compartment model with first-order absorption (with lag-time), linear elimination and combined errors adequately described lamotrigine PK data. Region was identified as a covariate for ka, sex was identified as a covariate for bioavailability (F), formulation was identified as a covariate for t-lag, and body weight was identified as a covariate for CL and V. Adding mixture model separating subpopulation with different CL was able to significantly reduce objective function value. Cross-study comparison suggested no major ethnic difference between Chinese and Caucasian subjects.

Conclusion: A mixture model was further supported when applying to the Chinese study dataset. No major ethnic difference was found between Chinese and Caucasians.

IV-74: *Meng Zhaoling* Program-wise trial simulation assessing design and analysis options from proof of concept to dose ranging

Zhaoling Meng, Tao Sheng, Dimple Patel, Hui Quan
Sanofi

Objectives: Getting the right dose(s) for Phase 3 program and market authorization is considered as one of the most difficult tasks in new drug development. A large percentage of drug development failures were attributed to an inappropriate dose selection at Phase 2. Often, a selected dose was later discovered with either a less favorable benefit-risk profile or less efficacy compared to competitors. In January 2014, EMA issued a qualification opinion paper recommending a MCP-mod approach (Multiple Comparison Procedure – Modelling) for a dose-response model-based design and analysis for Phase 2 dose ranging study (DRI). The paper highly promotes the exploration of the dose response curve in the early stage of the development to facilitate a better understanding of potential dose options for reaching a more informative decision. It advocates the importance of identifying the minimal effective dose (MED) under the current safety-centric drug development environment

Methods: We extended the MCP-mod approach to incorporate PK/Response modeling and potential even earlier dose-response exploration starting from the proof of concept study (POC). We used simulations under different assumed true underline dose-response profiles to compare different POC-to-DRI design and analysis scenarios including: a simple 2-arm (high dose vs. placebo) POC followed by a DRI analyzed by pair-wise between-treatment comparisons, a 2-arm POC followed by a DRI analyzed by MCP-mod, a 2-arm POC followed by a DRI analyzed by MCP-mod through PK/Response modeling. In addition, we compared scenarios of including multiple doses in a POC to obtain information and enhance DRI design potentially with reduced doses or better dose spacing.

Results: Based on the simulation results, PK/PD modeling can greatly increase the chance of identifying the MED. The benefit of early exploration of dose-response relationship with multiple doses in a POC study turns out to be scenario-dependent due to relatively high variability of small POC studies.

Conclusions: Therefore, a program-wise trial simulation is recommended to evaluate different POC-to-DRI designs under different compound specific assumptions.

IV-75: *Chenguang Zhou* Semi-mechanistic multiple-analyte pharmacokinetic model for a THIOMAB antibiotic conjugate against Staphylococcus aureus in mouse, rat and monkey

Chenguang Zhou, Siddharth Sukumaran, Montserrat Carrasco-Triguero, Ola Saad, Saroja Ramanujan, Amrita Kamath
Genentech, Inc., California, USA

Objectives: *Staphyloccocus aureus* (*S. aureus*) is a bacterial pathogen causing life threatening diseases such as bacteremia and bone infections. We have developed a novel THIOMAB™ antibiotic conjugate (TAC) to treat invasive *S. aureus* infections. The purpose of this study is to build a semi-mechanistic model to describe and predict the complex pharmacokinetic (PK) behavior of TAC.

Methods: The concentration-time profiles of two analytes, total antibody (Tab) and antibody-conjugated drug (acDrug), were quantified in mice (5, 25, or 50 mg/kg), rat (1, 25, or 50 mg/kg), and cynomolgus monkeys (1, 15, or 150 mg/kg) after a single intravenous (IV) dose of the anti-*S. aureus* TAC. A semi-mechanistic model was developed and parameter estimates were obtained by simultaneously fitting the model to all PK data at all dose levels for each species in MATLAB® SimBiology® software. The structure of the mathematical model was developed based on the known mechanisms of deconjugation and observed impact of drug-to-antibody ratios (DAR) on the PK of antibody-drug conjugates in general. Specifically, the model accounts for DAR dependent drug deconjugation and proteolytic degradation of TAC and was assessed by simultaneous fitting of different PK analytes.

Results: The same structure model described the observed Tab and acDrug concentration-time profiles in mouse, rat and monkey well. Final estimated parameters quantified the contribution of proteolytic degradation and deconjugation in clearing the conjugated drug, and suggested a similar drug deconjugation process across all three preclinical species.

Conclusions: This semi-mechanistic PK model improves our understanding of the complex PK behavior of the TAC in different species with translational application for human PK prediction.

References:
[1] Lu D, Jin JY, Girish S, Agarwal P, Li D, Prabhu S, Dere RC, Saad OM, Nazzal D, Koppada N, Ramanujan S, Ng CM. Semi-mechanistic Multiple-Analyte Pharmacokinetic Model for an Antibody-Drug-Conjugate in Cynomolgus Monkeys. Pharm Res. 2015; 32(6):1907-19.
[2] Sukumaran S, Gadkar K, Zhang C, Bhakta S, Liu L, Xu K, Raab H, Yu SF, Mai E, Fourie-O'Donohue A, Kozak KR, Ramanujan S, Junutula JR, Lin K. Mechanism-Based Pharmacokinetic/Pharmacodynamic Model for THIOMAB™ Drug Conjugates. Pharm Res. 2015; 32(6):1884-93.

IV-76: *Li Zhu* Population Pharmacokinetic Modeling of Ulocuplumab, an anti-CXCR4 Monoclonal Antibody in Patients with Relapsed/Refractory Acute Myeloid Leukemia and Multiple Myeloma

L Zhu, A Roy, P Statkevich, L Cohen, G Kroog, A Bello
Bristol-Myers Squibb Company

Objectives: Chemokine receptor 4 (CXCR4) is essential for homing and maintenance of hematopoietic stem cells in the bone marrow. Ulocuplumab (BMS-936564; ULO) is a first-in-class, fully human IgG4 monoclonal antibody, which inhibits the binding of CXCR4 to CXCL12. It is hypothesized that by mobilizing leukemic cells from the bone marrow to the peripheral blood, ULO could improve the response to chemotherapy. The objectives of the analysis were to develop a population PK model (PPK) for ULO and to identify key covariates in patients with hematological malignancies.

Methods: Data were assembled from 2 phase I multiple dose escalation studies in patients with relapsed/refractory acute myeloid leukemia (AML, N=73) and multiple myeloma (MM, N=35). ULO doses of 0.3, 1, 3 and 10 mg/kg were given weekly as 60-minute infusions. AML patients received 1 week ULO monotherapy followed by combination treatment with MEC (mitoxantrone/etoposide/cytarabine); MM patients received 2 weeks ULO monotherapy followed by combination with lenalidomide/dexamethasone or bortezomib/dexamethasone. A PPK model was developed using NONMEM (V7.2) in which body weight, gender, baseline albumin, white blood cell count (WBC), and combination chemotherapies were evaluated as covariates. A full model approach followed by a stepwise backward search was used for the covariate analysis.

Results: ULO serum concentration-time profiles and model diagnostics suggested concentration dependent disposition. A two-compartment model with parallel linear and nonlinear elimination pathways adequately described the data. Central (Vc) and peripheral volume of distribution were 4.37 L (%RSE: 3%) and 3.6 L (16%) respectively; the linear clearance (CL) was 0.015 L/h (9%) and the maximum nonlinear clearance was 0.29 L/h (Vmax/Km). WBC, which expresses the target CXCR4 receptor, was influential on Vmax. In the full model, the allometric coefficients of body weight for ULO CL and Vc were estimated to be 0.33 and 0.41, respectively, suggesting a modest effect of body weight. Simulations indicated that an ULO flat dosing regimen could provide relatively uniform exposures over a wide body weight range.

Conclusions: ULO PK was well described by a PPK model with parallel linear and nonlinear elimination. Covariate analysis indicated a modest effect of body weight. The population PK model provided the basis for evaluating flat dosing regimens in additional clinical studies.

IV-77: *Kirill Zhudenkov* A Markov Chain model to characterize cataract progression and disease burden in the Russian Federation

Kirill Zhudenkov (1), Olga Orlova (2), Blair Ireland, Vladimir Trubilin (2)
(1) – M&S Decisions, Moscow, Russia; (2) - The Institute of Improvement of Professional Skill of the Federal Medico-Biological Agency of Russia

Objectives: Cataract - clouding of the eye lens, resulting in blurred vision - is a slowly but irreversibly progressing disease; it may result in complete blindness. The ophthalmic market in Russia is rapidly growing. However, among patients, ophthalmologists, and health authorities, there is broad heterogeneity in knowledge of cataract treatment options and in opinions on the utilization of modern treatment techniques. The aim of this work was to provide a model-based analysis that represents cataract progression and disease burden in Russia, in order to compare costs of (i) conservative and non-effective treatment (eye drops) vs. (ii) surgical and more effective treatments.

Methods: The disease progression model implied a Markov Chain, with 4 states of vision quality, from normal vision to severe cataract and transition probabilities fitted against the epidemiology study data [1, 2] and official Russian statistics [3-5]. The model estimates disease progression, quality-of-life changes, direct and indirect treatment costs, in 50- to 80-year old patients. Cataract surgery outcomes and complications were also taken into account.

Results: The model allowed us to estimate disease progression rate, as related to the continuous loss of vision observed at different stages of cataract development. For example, the model suggested that, at around 50 years of age, about 15% of individuals within the considered cohort would be diagnosed with cataract; at age 60, this fraction would raise up to 50%. From a cost effectiveness standpoint, model-based results indicate that direct and indirect costs of conservative treatment, which are initially much smaller vs. surgery cost, exceed direct costs related to surgical treatment, 4 to 8 years post diagnosis.

Conclusions: We provide here a new, quantitative, model-based paradigm for cataract burden & treatment option assessments, through the implementation of a qualified disease progression model and a cost / quality-of-life analysis. Costs of conservative (and rather non-efficacious) treatment, while initially modest, do exceed surgery cost within a relatively short period of time following diagnosis and while individuals are still part of the active work force, thus favoring the more efficacious, and ultimately more cost-effective treatment (surgery). These results are expected to provide a rational support for the wider use of cataract surgery in Russia, both in the private market as well as in state-funded medical care.

References:

[1] J Epidemiol Biostat. 1999;4(4):337-44;
[2] Eur J Ophthalmol. 2010 Sep-Oct;20(5):892-901;
[3] The data from the Moscow Federal fund for OMS 2015. http://www.mgfoms.ru;
[4] The data from the General OMS Tariff agreement 2013;
[5] The data from the Federal Statistics Service in Russia 2015. http://www.gks.ru

IV-78: *Jochen Zisowsky* A Method to Perform PK-QT Analyses When Several Active Compounds or Metabolites Are Present

Jochen Zisowsky, Noelia Nebot, Guenter Heimann
Pharmacometrics Unit, Oncology Clinical Pharmacology, Novartis Pharma AG

Objectives: To develop a statistically sound approach for PK-QT analysis when jointly modeling the impact of two active compounds by developing confidence region for the expected effect at maximum concentration (Cmax) of the two compounds which excludes an effect of 10 msec or larger, corresponding to controlling the type I error for an appropriately defined hypothesis test.

Methods: PK and QT data were obtained from a single arm trial in patients. The primary endpoint was ddQTcF defined as time-matched change from baseline in QTcF. The lme() function in R 3.0.2 was used to develop a model which was linear in both compounds (without/with interaction) and included a fixed effect parameter for the diurnal effect, and a random patient effect. This model can be viewed as an extension of the model proposed by Hosmane et al.[1] for a single agent to the situation with two active drugs.

The effect of Cmax (either from the individual bivariate PK data or at the respective Tmax) was evaluated for each compound by plugging Cmax into the model equation. We used bootstrap to test the null hypothesis whether the expected effect at Cmax would be ≥10 msec. The null hypothesis was rejected if the proportion of bootstrap copies with an estimated effect >10 msec was

Results: PK profiles of the four compounds could be grouped into two pairs with similar PK behavior and the subsequent PK-QT analysis could be simplified to two compounds. The PK-QT analysis revealed competing effects of two compounds on QT. The estimated effect at Cmax was

None of the observed concentration pairs were above the 10 msec line and none of the 95% ellipsoids representing the joint two-dimensional distribution of the pairs of maximum concentrations crossed the 10 msec line.

Conclusions: The developed approach to analyse PK-QT data when two active compounds are present worked well in our data example. The reduction of QT interval by the parent compound and the increase of QT interval by the second compound were nicely reflected in our parameter estimates. This contradicting effect would have shown as hysteresis in a separate PK-QT analysis for each compound, leading to biased and not interpretable results. Our two-dimensional approach nicely overcomes this issue.

References:
[1] Hosmane B, Locke C, Chiu YL. Exposure-Response Modeling Approach for Assessing QT Effect in Thorough QT/QTc Studies. J Biopharm Stat (2010) 20(3): 624-640.

S-01: *Kajsa Harling* PsN and Xpose

Kajsa Harling, Andrew C. Hooker, Rikard Nordgren and Mats O. Karlsson
Pharmacometrics group, Department of Pharmaceutical Biosciences, Uppsala University, Sweden

PsN is a toolbox for population PK/PD model building using NONMEM 6 and 7. It has broad functionality ranging from results extraction from output files to advanced computer-intensive statistical methods. Updates since PAGE 2015 include major extensions to **sir**, a tool for fast and robust assessment of parameter uncertainty with automatically generated visual diagnostics of convergence and parameter confidence intervals, **simeval**, a tool for simulation-evaluation diagnostics for outlier detection, and **benchmark**, a tool for simple comparisons of estimation results and approximate run times across combinations of NONMEM options, Fortran compiler and NONMEM versions.

Xpose 4 is an open-source population PK/PD model building aid for NONMEM. Xpose attempts to facilitate the use of diagnostics in an efficient manner, providing a toolkit for dataset checkout, exploration and visualization, model diagnostics, candidate covariate identification and model comparison.

Xpose has customized functions for generating plots based on PsN output, and several of them can be automatically run by adding the -rplots option to the PsN command. This gives pdf documents with, for example, visual predictive checks as part of the PsN output, without the need to manually run any R script.

Both PsN and Xpose are freely available at http://psn.sourceforge.net and at http://xpose.sourceforge.net

Acknowledgments: This work was supported in part by the DDMoRe (www.ddmore.eu) and IDeAl (www.ideal.rwth-aachen.de) projects.

References:

[1] Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Computer Methods and Programs in Biomedicine. 58(1):51-64.
[2] Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)--a Perl module for NONMEM related programming. Comput Methods Programs Biomed. 75(2):85-94.
[3] Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 79(3):241-57.
[4] Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol. (2013) 2, e50.
[5] Dosne AG, Bergstrand M, Karlsson MO. Application of Sampling Importance Resampling to estimate parameter uncertainty distributions. PAGE 22 (2013) Abstract 2907.
[6] Dosne AG, Bergstrand M, Karlsson MO. Determination of Appropriate Settings in the Assessment of Parameter Uncertainty Distributions using Sampling Importance Resampling (SIR). PAGE 24 (2015) Abstract 3546.
[7] Largajolli A, Jönsson S, Karlsson MO. The OFVPPC: A simulation objective function based diagnostic. PAGE 23 (2014) Abstract 3208.

S-02: *Gaohua Lu* Simcyp Simulator

The Simcyp consortium
Simcyp

Simcyp Simulator - a user-friendly IVIVE-PBPK platform and database for mechanistic modelling, simulation and prediction of drug absorption, tissue distribution, metabolism, transport, elimination and drug-drug interactions in healthy and disease populations using in vitro and in vivo knowledge and PBPK modelling technology

Developing a user-friendly platform that can handle a vast number of complex physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) models both for conventional small molecules and larger biologic drugs is a substantial challenge. The Simcyp Population Based Simulator is currently used by the majority of large pharmaceutical companies (70% of top 40 - in term of R&D spending) and has impacted more than 20 NDA labelling packages in the past 3 years.

Under the guidance of the Simcyp consortium the Simulator has evolved from a simple drug-drug interaction tool to a sophisticated and comprehensive PBPK-Model-Informed Drug Development (PBPK-MIDD) platform that covers a broad range of applications spanning from early drug discovery to late drug development, from small molecules to large molecules including antibody-drug conjugates (ADC), encompassing PBPK models for simulating drug disposition in pre-clinical species (mouse, rat, dog and monkey) and in a variety of human populations (including adult Caucasian, Japanese and Chinese populations as well as paediatric, pregnancy, obesity, hepatic and renal impairment populations).

In the demonstration session we will provide an update on the latest architectural and implementation developments within the small molecule and biologics simulators, as well as offering demonstrations of SIVA (Simcyp In vitro Data Analysis Tool) and CSS (Cardiac Safety Simulator).

Some details of the scientific background to Simcyp's approaches can be found in our recent publications:

Prediction of drug-drug interactions arising from CYP3A induction using a physiologically-based dynamic model.
Almond LM, Mukadam S, Gardner I, Okialda K, Wong S, Hatley O, Tay S, Rowland-Yeo K, Jamei M, Rostami-Hodjegan A, Kenny JR. Drug Metab Dispos. 2016 Mar 29. pii: dmd.115.066845

Metformin and cimetidine: Physiologically based pharmacokinetic modelling to investigate transporter mediated drug-drug interactions.
Burt HJ, Neuhoff S, Almond L, Gaohua L, Harwood M, Jamei M, Rostami-Hodjegan A, Tucker GT, Rowland-Yeo K. Eur J Pharm Sci. 2016 Mar 24. pii: S0928-0987(16)30093-8. doi: 10.1016/j.ejps.2016.03.020.

Considering Age Variation when Coining Drugs as High vs Low Hepatic Extraction Ratio.
Salem F, Abduljalil K, Kamiyama Y, Rostami-Hodjegan A. Drug Metab Dispos. 2016 Feb 10. pii: dmd.115.067595.

A Bottom-Up Whole-Body Physiologically Based Pharmacokinetic Model to Mechanistically Predict Tissue Distribution and the Rate of Subcutaneous Absorption of Therapeutic Proteins.
Gill KL, Gardner I, Li L, Jamei M. AAPS J. 2016 Jan;18(1):156-70. doi: 10.1208/s12248-015-9819-4.

S-03: *William Knebel* Metworx: high-performance cloud computing made simple

Bill Knebel, Jeff Hane, Dan Polhamus, Marc Gastonguay
Metrum Research Group

METWORX is high-performance cloud computing made simple. On-demand and with just a few clicks, METWORX will build and configure your grid infrastructure, ready to use from the convenience of a web browser. Users connect seamlessly to the RStudio or PiranaJS workspaces, all without leaving the web browser environment. The METWORX family of products includes METWORX Packs which provide detailed instructions and code examples for specialized analysis.

METWORX features include:

Autoscaling which enables users to select a lower and upper Workflow cluster size and the system automatically scales up and down based on demand.

Enhanced Dashboard showing change in cluster size, memory usage, and pending jobs.
Ability to resize your encrypted EBS volumes (your virtual hard disk for analysis and data storage) during Workflow creation.

Custom-built web apps (METWORX Envision) that allow non-technical users and decision makers to perform on-the-fly simulations, decision-path exploration, and visualization of model results, all in real time.

S-04: *Robert Bauer* NONMEM® 7.3 and 7.4 and PDx-Pop® 5.2

Robert J Bauer
ICON Clinical Research LLC

Please stop by at our booth at PAGE 2016 to learn of the present release of NONMEM 7.3, our upcoming features in NONMEM 7.4, and our just released version of PDx-Pop 5.2.

ICON is committed to providing the most advanced analysis methods and tools for the pharmaceutical industry through continued enhancements to the NONMEM® software, the industry standard for population pharmacokinetic/pharmacodynamics analysis; ensuring pharmaceutical companies may continue to use this trusted analysis tool, incorporating classical as well as new analysis algorithms for present day pharmaceutical development. In addition, PDx-Pop™, a graphical interface working in concert with NONMEM®, integrates with existing tools and its own automated methods to expedite population modeling and analysis, providing optimal flexibility, increased efficiency and functionality.

NONMEM® – Continuous Enhancements:

NONMEM® has been relied on by the PK/PD modeling community for over 30 years, so ICON understands the importance of continuously improving this trusted tool for analysing Population Pharmacometric data. Statistical analysis with NONMEM helps sponsors determine appropriate dosing strategies for their products, and increases their understanding of drug mechanisms and interactions. With NONMEM's new features, such as algorithms that improve the performance of Monte Carlo and classical estimation methods, the information needed for critical decision- making will be available faster and more efficiently.

The latest release of NONMEM is 7.3, incorporating the following enhancements:

- More efficient memory allocation for sizing problems, particularly for huge models with many parameters to be estimated.
- More mixed effects levels, with random effects across groups of individuals such as clinical site, may now be modeled. Sites themselves may be additionally grouped, such as by country, etc.
- Algorithms to assess optimal settings for Monte Carlo estimation methods.
- Algorithms to aid in global optimization of classical estimation methods.
- Expanded language facilities for the control stream file, such as handling repetitive code, symbolic references to indexed parameters, extending code across lines, up to 67000 characters.
- Built-in bootstrap algorithms with stratification.
- Enhanced non-parametric analysis methods.

We are presently developing NONMEM 7.4. Some of the new features are:

- Parallelization extended to additional tasks
- Improved Speed for FOCE/ITS Analyses
- Improvements in IMP, SAEM and BAYES Analysis
- Additional Table Output Control: Specific control of which records to be outputted
- Further Symbolic Code enhancement of control stream code
- Read MSF files Generated from Earlier Versions of NONMEM
- Preconditioning and SIR sampling of Covaraince of extimates assessment

PDx-Pop® – Visual Companion for NONMEM, Expediting Population Analysis:

Just released is Pdx-Pop 5.2, fully compatible with NONMEM 7.3:

- Control Stream, PK and User (including ODE) Modeling and Advanced Methods Wizards to assist in model development and MU referencing
- Multi-Processor Capability for Batched Runs of multiple control stream files
- Extended summary output of including estimated population parameters and relative standard error, and goodness of fit statistics
- Automated R/S-Plus plots of diagnostic plots, estimated parameters (qqplots, histograms) and etas (pairs plots, histograms), Bayesian parameter sampling history plots
- Access Custom User-written R/S-Plus scripts from PDx-Pop
- Automated classical, standardized, and prediction corrected Visual Predictive Check.
- Easy Multi-processor distribution of bootstrap runs, using NONMEM 7.3's built-in bootstrap algorithm.

S-05: *Thomas Eissing* PK-Sim and MoBi for PBPK and Quantitative Systems Pharmacology Modeling and Simulation

Eissing, Thomas (1); Hobe, Martin (2); Ince, Ibrahim (1); Solodenko, Juri (1); Teutonico, Donato (1); Wendl, Thomas (1)
(1) Bayer Technology Services, Leverkusen, Germany, (2) Bayer Pharma, Wuppertal, Germany

The Bayer Computational Systems Biology Software Suite contains different software tools and has been designed using a modular concept to allow efficient multi-scale modeling and simulation [1]. The central software tools are PK-Sim® and MoBi®. While PK-Sim® is focused on whole-body physiologically-based pharmacokinetic (PBPK) modeling, MoBi® provides a flexible modeling environment fully compatible with PK-Sim®, for model customization or extension including pharmacodynamic or systems pharmacology modeling.

PK-Sim® is a comprehensive software tool for whole-body PBPK modeling of small and large molecules. It enables rapid access to all relevant anatomical, physiological, and molecular parameters for humans (age-dependent) and the most common laboratory animals (mouse, rat, minipig, dog, and monkey) that are contained in the integrated database. Moreover, easy access to different PBPK calculation methods and template building blocks allows for fast and efficient model building and parameterization. Relevant passive processes for drug absorption, distribution, metabolization and elimination (ADME) are automatically taken into account by PK-Sim®. Specific active processes such as metabolization by a certain enzyme, transport, or target binding can be conveniently added. For a large set of enzymes, transporters and other proteins, information on expression profiles and ontogeny information is contained in the software database. Different models can be combined to allow parent-metabolite or drug-drug interaction (DDI) modeling. In order to facilitate DDI modeling, a growing number of predefined templates for interaction partner substances are integrated. PK-Sim® is designed for use by non-modeling experts and only allows for minor structural model modifications.

MoBi® is a systems biology software tool for multiscale physiological modeling and simulation. Within the restrictions of ordinary differential equations, almost any kind of (biological) model can be imported or set up from scratch. Examples include biochemical reaction networks, compartmental disease progression models, or PBPK models, e.g. imported from PK-Sim. Importantly, MoBi® also allows for the combination of the described examples and thereby is a very powerful tool for modeling and simulation of multiple physiological scales and systems covering molecular details on the one hand and whole-body architecture on the other hand.

Apart from the two central graphical user interface (GUI) based software tools PK-Sim® and MoBi®, the software platform has a common core, import and export options including SBML and MS Excel®, as well as interfaces to the general computing environments MATLAB® and R. The toolboxes can be used to access and modify model parameters as well as to execute simulations and retrieve results. That way, the toolboxes can be used to script or code batch simulations, analysis tasks, visualizations or customized workflows to any complexity.

Optimization-based parameter identification or population simulations can be conveniently performed using integrated guided workflows. Tracking and roll-back features embedded in an automated project history, model comparison functions as well as a project journal for additional documentation allow for full traceability and transparency.

In summary, the software platform with its core components PK-Sim® and MoBi® provides a very flexible, comprehensive and transparent systems pharmacology modeling and simulation environment to challenge the consistency of data and allow for the integration and translation of knowledge to support modern drug research and development [2].

References:

[1] Eissing T. et al. A computational system biology software platform for the multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front. Physio. (2011)
[2] www.systems-biology.com