Tuesday June 7

08.00-19.00	**Registration at Hotel Divani Caravel**	
19.00-21.00	**Opening Ceremony at the Hotel Divani Caravel (Olympia hall), continued with cocktails at the hotel's roof garden by the pool**	

Wednesday June 8

07:00-08:45	**Registration**	
08:45-09:00	**Welcome and Introduction**	
09:00-10:00	**PKPD-modelling in Multiple Sclerosis and Infection**	*chair: Panos Macheras and Aris Dokoumetzidis*
09:00-09:20	*Pascal Girard*	A Semi-mechanistic Model of Lymphocyte Dynamics in Patients with Multiple Sclerosis Treated with Cladribine Tablets
09:20-09:40	*Mats Karlsson*	Population Pharmacodynamics of Cladribine Tablets Therapy in Patients with Multiple Sclerosis: Relationship between Magnetic Resonance Imaging and Clinical Outcomes
09:40-10:00	*Bambang Adiwijaya*	An integrated, mechanistic model of viral eradication and its clinical applications in treatment regimens with direct-acting antivirals for chronic hepatitis C
10:00-10:15	***Lutz Harnisch and Mats Karlsson***	**Presentation of DDMoRe**
10:15-11:45	**Coffee break, Poster (Ilissos) and Software (Olympia foyer) session I**	
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter	
11:45-12:30	**Time to event Tutorial (I)**	*chair: France Mentré*
11:45-12:30	*Nick Holford and Marc Lavielle*	A tutorial on time to event analysis for mixed effect modellers
12:30-14:00	**Lunch: Amalia hall (Level 0) and Constantinople Restaurant (Lobby Level)**	
14:00-14:55	**Time to event Tutorial (II)**	*chair: Nick Holford*

14:00-14:55	*Alan Kimber*	Parametric time to event methods incorporating time dependent covariates
14:55-16:10	**Tea break, Poster (Ilissos) and Software (Olympia foyer) session II**	
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter	
16:10-17:30	**Stuart Beal Methodology Session: Modelling strategies**	*chair: Lutz Harnisch*
16:10-16:30	*Chuanpu Hu*	Informative Dropout and Visual Predictive Check of Exposure-Response Modeling of Ordered Categorical Data
16:30-16:50	*Marc Gastonguay*	Full Covariate Models as an Alternative to Methods Relying on Statistical Significance for Inferences about Covariate Effects: A Review of Methodology and 42 Case Studies.
16:50-17:10	*Céline Laffont*	How to analyse multiple ordinal scores in a clinical trial? Multivariate vs. univariate analysis.
17:10-17:30	*Julie Bertrand*	Some Alternatives to Likelihood ratio and Wald Tests for Pharmacogenetic studies using nonlinear mixed effect models.

Thursday June 9

08:30-09:50	**Lewis Sheiner Student Session**	*chairs: An Vermeulen, Alison Thomson, Niclas Jonsson, Malcolm Rowland*
08:30-08:55	*Abhishek Gulati*	Linking in silico and in vitro experiments to identify and evaluate a biomarker for enoxaparin activity
08:55-09:20	*Joshua Pink*	Pharmacokinetic-pharmacodynamic-pharmacoeconomic analysis of rituximab for follicular lymphoma
09:20-09:45	*Elodie Plan*	Modelling Techniques Handling Dynamic Pain Scores Characteristics
09:45-09:50	**Presentation of Awards**	
09:50-11:05	**Coffee break, Poster (Ilissos) and Software (Olympia foyer) session III**	
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter	
11:05-12:15	**PBPK**	*chair: Marylore Chenel*
11:05-11:55	*Malcolm Rowland*	Physiologically based pharmacokinetics: Advancing the clinical dimension
11:55-12:15	*Ashley Strougo*	Scaling pharmacokinetics to estimate the “first dose in children”: comparing allometric scaling and PBPK

12:15-13:45	**Lunch: Amalia hall (Level 0) and Constantinople Restaurant (Lobby Level)**	
13:45-15:05	**PKPD-modelling of tumour effects and adverse events for anticancer drugs**	*chair: Dinesh De Alwis*
13:45-14:05	*Benjamin Ribba*	Evaluation of the antitumor effect of PCV chemotherapy on low-grade gliomas patients with a longitudinal tumor growth inhibition model
14:05-14:25	*Emma Hansson*	PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3 and sKIT as Biomarkers of Tumor Response and Overall Survival Following Sunitinib Treatment in GIST
14:25-14:45	*Inès Paule*	Individual Prediction-Based Dose Adaptation Of Capecitabine: In Silico Comparison With The Standard Method, Impact On Limiting Toxicity and On Antitimour Efficacy
14:45-15:05	*Coen van Hasselt*	Optimizing monitoring strategies of trastuzumab induced cardiotoxicity: Development and application of a population pharmacodynamic model quantifying trastuzumab induced changes in cardiac function
15:05-16:20	**Tea break, Poster (Ilissos) and Software (Olympia foyer) session IV**	
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter	
16:20-17:20	**Design**	*chair: Steve Duffull*
16:20-16:40	*Lee Kien Foo*	Cost minimization of a phase IIA clinical study
16:40-17:00	*Sebastian Ueckert*	Explicit Optimization of Clinical Trials for Statistical Power
17:00-17:20	*Peter Gennemark*	Optimal design in population kinetic experiments by set-valued methods
20:00-01:00	**Social evening**	

Friday June 10

09:00-10:20	**Target-mediated drug disposition**	*chair: Charlotte Kloft*
09:00-09:40	*Leonid Gibiansky*	Modeling of Drugs with Target-Mediated Disposition
09:40-10:00	*Stefaan Rossenu*	Population Pharmacokinetic/Pharmacodynamic Modeling of a New Antithrombotic Drug, The Nanobody® ALX-0081
10:00-10:20	*Angelica Quartino*	An integrated G-CSF-myelosuppression model characterizing the target mediated disposition of endogenous G-CSF in breast

cancer patients following chemotherapy

10:20-10:30	**Preview of PAGE 2012**	
10:30-10:40	**Preview of WCoP 2012**	
10:40-11:10	**Coffee Break**	
11:10-12:30	**Modelling and methods for complex systems**	*chair: Oscar Della Pasqua*
11:10-11:30	*Stephan Schmidt*	Coping with Time Scales in Disease Systems Analysis: Application to Bone Remodelling
11:30-11:50	*Elba Romero*	Coupling complex mechanistic PK/PD modelling with dynamic system analysis to obtain relevant clinical/biological insights. Application to gonadotropin hormone release agonist
11:50-12:10	*Wojciech Krzyzanski*	Solving Delay Differential Equations in S-ADAPT by Method of Steps
12:10-12:30	*S. Y. Amy Cheung*	Structural identifiability of parallel pharmacokinetic experiments as constrained systems
12:30-12:40	**Closing Remarks**	
12:40-12:55	**Audience Input for the PAGE 2012 Program**	

Software demonstrations: **Olympia foyer (Level -1)**

Kajsa Harling Perl speaks NONMEM (PsN) and Xpose
Marc Lavielle Analysing population PK/PD data with MONOLIX 4.0
Joakim Nyberg PopED - An optimal experimental design software
Coen van Hasselt Piraña: The flexible modeling environment for NONMEM
Stephane Vellay Pipeline Pilot - Data Integration, Analysis, and Reporting Platform

Posters: Absorption and physiology-based PK

I-10 *Christian Bartels* Population PK Model for Pooled Data of Different Oral Diclofenac Formulations
I-35 *Vicente G. Casabo* Bioequivalence trials simulation to select the best analyte for acetylsalicylic acid
I-62 *Kristin Dickschen* Pharmacogenomics of Tamoxifen In Female Patients: A PBPK Model-based Investigation Including The Three Main Metabolites
II-20 *Ludivine Fronton* Monoclonal Antibody Disposition beyond Target Binding: Impact of FcRn on Clearance and Derivation of Mechanistic Compartment Models

II-40 *Emilie Hénin* Meta-analysis of Magnetic Marker Monitoring data to characterize tablet movement through the gastrointestinal tract
III-9 *Donghwan Lee* Development of a population model to describe diurnal and chronokinetic variation in cilostazol pharmacokinetics
III-26 *Eugeniy Metelkin* A Systems Pharmacology Model of Anandamide Dynamics After FAAH Inhibitor Administration
III-35 *Christoph Niederalt* Development of a detailed physiologically based computational kidney model to describe the renal excretion of hydrophilic agents in rats
III-40 *Kayode Ogungbenro* A semi-mechanistic gastric emptying pharmacokinetic model for 13C-octanoic acid: an evaluation using simulation
III-54 *Anna Pieper* Development of a PBPK model of doxorubicin
IV-8 *Alexander Solms* Modelling Inter-Individual Variability in PBPK Models and Deriving Mechanistic Covariate Models for PopPK
IV-21 *Sonya Tate* The Importance of Enterohepatic Recirculation in the Disposition of Pravastatin and Rosuvastatin: A Physiologically-Based Pharmacokinetic Modelling Approach
IV-47 *Thomas Wendl* Development of a physiologically-based pharmacokinetic (PBPK) model for Moxifloxacin and its metabolites in healthy adults
IV-65 *Kirill Zhudenkov* Pharmacokinetics of PEG-IFN Alpha in HCV Infected Patients

Posters: Cardiovascular, QT-prolongation

I-14 *Francesco Bellanti* Relevance of QT-RR correlations in the assessment of QTc-interval prolongation in clinical trial simulations
I-28 *Christine Brandquist* PK/PD Modeling of the Effect of Intravenous Doses of Anzemet® (dolasetron mesylate) and Its Metabolite (hydrodolasetron) on the QT Interval in Healthy Subjects
I-37 *Anne Chain* Can First-Time-In-Human Trials Replace Thorough QT Studies?
I-63 *Jeroen Diepstraten* Pharmacodynamics of nadroparin using anti-Xa levels in morbidly obese patients upon subcutaneous administration of 5700 IU
II-1 *Vincent Dubois* Translation of drug-induced QTc prolongation in early drug development.
II-11 *Farkad Ezzet* Meta-Analysis of Antiplatelets in Patients with Atrial Fibrillation: A survival Model
II-44 *Eleanor Howgate* PKPD Modelling Of Cardiovascular Safety Pharmacology Data
II-55 *Helene Karcher* Probabilistic risk assessment for QT prolongation and heart rate increase
III-41 *Oliver Ackaert* Population modelling of blood pressure: assessing clinically important factors for cardiovascular diseases
IV-6 *Nelleke Snelder* Quantitative understanding of drug effects on the interrelationship between mean arterial blood pressure, cardiac output and total peripheral resistance
IV-36 *Piet van der Graaf* Towards a Thorough Preclinical QT ("TpQT") study paradigm: Pharmacokinetic-Pharmacodynamic (PKPD) Modelling of QTc Effects of Moxifloxacin in Cynomolgus Monkeys

Posters: CNS

I-22 *Irina Bondareva* Sequential Interacting Multiple Model (IMM) Bayesian Analysis of Carbamazepine and Valproate Repeated Therapeutic Drug Monitoring (TDM) Data from Epileptic Patients
I-32 *Jacob Brogren* Separate vs. simultaneous analysis of co-primary endpoints in Alzheimer's disease clinical trials
I-56 *Elizabeth de Lange* Mechanism-based PK-PD model of remoxipride with rat-to-human

extrapolation: characterizing remoxipride target site PK and systems homeostatic feedback
II-25 *Martin Gnanamuthu Johnson* Predicting Dopamine D2 Receptor Occupancy in humans using a physiology-based approach
II-26 *Martin Gnanamuthu Johnson* Pharmacokinetic-Pharmacodynamic Modeling of Dopamine D2 Receptor Occupancy in humans using Bayesian modeling tools
II-34 *Zheng Guan* Population pharmacokinetic and pharmacodynamic analysis of cortisol in serum and saliva in healthy male volunteers after an acute 5-hydroxytryptophan (5-HTP) challenge test
II-42 *Eef Hoeben* Population pharmacokinetic analysis of JNJ-37822681, a specific and fast-dissociating D2 antagonist for the treatment of schizophrenia
II-48 *Masoud Jamei* A physiologically-based pharmacokinetic (PBPK) brain model and its application in simulating drug disposition in brain
II-65 *Huub Jan kleijn* Development and Application of a Semi-Mechanistic Model for Modulation of Amyloid-beta in Cerebrospinal Fluid after Inhibition of γ-secretase.
III-16 *Arianna Madrid* Modelling the sleep effects of Zolpidem in rats using non-homogeneous Markov chain models
III-25 *François Mercier* A Bayesian meta-analysis of longitudinal lesion count data in multiple sclerosis patients
III-56 *Venkatesh Pilla Reddy* Exposure-Response Relationship of Typical and Atypical Antipsychotics Assessed by the Positive and Negative Syndrome Scale (PANSS) and its Subscales
III-58 *Bart Ploeger* Confirmation of symptomatic and disease modifying effects of levodopa using the ELLDOPA study
IV-15 *Ahmed Suleiman* A Mixed-Effects Markov Model for Characterizing the Time Course of the Transitions between Different Extrapyramidal Side Effects Severity Levels
IV-19 *Stina Syvänen* Quinidine Microdialysis Reveals Altered P-glycoprotein Function in Epileptic Rats in the Brain Parenchyma Rather than at the Blood-Brain Barrier
IV-30 *Karin Tunblad* A pharmacokinetic/pharmacodynamic analysis of central and peripheral effects of GSK3 inhibitors

Posters: Endocrine

I-45 *Steve Choy* Application of an integrated glucose-insulin model to investigate the effects of glibenclamide and its active metabolites on postprandial glucose and insulin concentrations in healthy volunteers
II-7 *Petra Ekerot* Mechanism-based Pharmacokinetic-Pharmacodynamic Feedback Model of Thyroid Hormones after Inhibition of Thyroperoxidase in the Dog. Cross-species Prediction of Thyroid Hormone Profiles in Rats and Humans.
III-6 *Anna Largajolli* Meal Tolerance Test (MTT): Nonlinear Mixed-Effects Modeling of Insulin Secretion
III-29 *Jonas Bech Møller* Model-based Analysis of the GLP-1 Response following an Oral Glucose Tolerance Test (OGTT)
III-46 *Joanna Peng* A Mechanistic Model for the Effects of A Novel Drug on Glucose, Glucagon and Insulin Applied to Adaptive Phase II Design
III-49 *Kirill Peskov* A Quantitative Systems Pharmacology Model Provides Insights into Phosphate Homoeostasis through Multiple Interacting Pathways
IV-37 *Piet van der Graaf* Application of a Multiscale Physiologically-Based Bone and Calcium Systems Model to Guide the Development of GnRH receptor modulators for the Management of Endometriosis
IV-59 *Stefan Zajic* Semi-mechanistic PK/PD Model of the Effect of Odanacatib, a Cathepsin K

Inhibitor, on Bone Turnover to Characterize Lumbar Spine and Distal Forearm Bone Mineral Density in Two Phase II Studies of Postmenopausal Women

Posters: Estimation methods

I-29 *Karl Brendel* A comparison of MONOLIX, NONMEM 6 and NONMEM 7 based on a simulated PK example
I-40 *Ng Chee* Novel GPU-based Parallelized Qausi-random Parametric Expectation-Maximization (QRPEM) Estimation Method for Population Data Analysis
I-44 *Jason Chittenden* Evaluation of the Lindstrom-Bates FOCE Algorithm with Simulated Pharmacokinetic Datasets
I-50 *Emmanuelle Comets* SAEMIX, an R version of the SAEM algorithm
I-54 *Alexander Danis* Set-valued methods for estimation of parameters in population models
II-29 *Helen Graham* Development of a novel method for updating the predicted partition coefficient values generated by an existing in silico prediction method
III-8 *Robert Leary* Exact Reproducibility of Population PK/PD NLME Numerical Results across Different Computational Environments
III-42 *Erik Olofsen* Population Analysis of Kalman-Filtered Permutation Entropy of the Electroencephalogram
III-43 *Itziar Oteo* Differences among six prevalent creatinine clearance calculation methods by covariate modeling of CL for Netilmicin using NONMEM for inference
IV-41 *Georgios Vlasakakis* The impact of modified-release formulations on bridging of pharmacokinetic data from adults to children

Posters: Infection

I-2 *Mona Alameddine* Population Pharmacokinetic Analysis and Effects of Raltegravir In HIV positive and Healthy Individuals
I-3 *Sarah Alghanem* Development of a Tobramycin Dosage Adjustment Nomogram for Patients with Cystic Fibrosis
I-16 *Julie Bertrand* Extensive Population Pharmacokinetic-Pharmacogenetic Study of Nevirapine in HIV-Infected Cambodian Patients
I-30 *Margreke Brill* Cefazolin pharmacokinetics in morbidly obese patients following a prophylactic dose during weight reducing surgery.
I-39 *Georgia Charkoftaki* Pharmacokinetics of doripenem in cerebrospinal fluid
I-46 *Christine Xu* Population Pharmacokinetics (PPK) and Pharmacokinetic-Pharmacodynamic (PK/PD) of Vicriviroc in Treatment Naive HIV
I-60 *Paolo Denti* Population PK of Isoniazid in South African Adults.
II-17 *Monika Frank* Integrated Population Pharmacokinetic Model Development of Nevirapine for Mothers and Newborns including Healthy Male Volunteer Data
II-22 *Maria Garrido* Population Pharmacokinetics/Pharmacodynamics of Ganciclovir after Intravenous Ganciclovir and Oral Valganciclovir Administration in SOT Patients Infected with CMV
II-27 *Sylvain Goutelle* Comparison of Four Renal Function Estimator-Based Models for the Prediction of Gentamicin Concentrations in Geriatric Patients by Use of Nonparametric Population Approach
II-35 *Monia Guidi* Population Pharmacokinetics of Nevirapine in HIV-positive Patients
II-43 *Richard Höglund* Population modelling of the pharmacokinetics of a mefloquine-artesunate treatment at the Thai-Myanmar border
II-46 *Arantxa Isla* Population Pharmacokinetics of Cefoxitin as a Prophylactic Antimicrobial

Agent
II-60 *Dalia Khachman* Optimising ciprofloxacin dosing in intensive care patients based on pharmacodynamic target attainment
II-61 *David Khan* PKPD-modeling of time-kill curves from E. coli mutants exposed to ciprofloxacin
III-5 *Ryuji Kubota* A Novel Framework of Long-term Prediction of integrase inhibitors for treatment naïve patients
III-36 *Elisabet Nielsen* PK/PD Indices of Antibiotics Predicted by Mechanism-Based PKPD Models
III-63 *Dinko Rekic* Bilirubin - a biomarker of atazanavir exposure in HIV/AIDS patients
IV-4 *Andre Schäftlein* Comparison of elimination and absorption pharmacokinetics of linezolid in cystic fibrosis patients by three nonlinear models
IV-9 *Ivy Song* Applications of Population Pharmacokinetic Modeling during Phase2B to Support the Clinical Development of Dolutegravir (DTG, S/GSK1349572)
IV-12 *Joe Standing* Methods for Optimising Neonatal Antimicrobial Use: Time- and Concentration-Dependent Agents
IV-16 *Elin Svensson* Mega-model of nevirapine population pharmacokinetics
IV-17 *Vinogradova Svetlana* Applying of population PK-PD methods to analysis of viral dynamics of HIV/HCV-Coinfected Sustained Virological Responders and Nonresponders treated with PEG-IFN
IV-18 *Ami Fazlin Syed Mohamed* Pharmacokinetic-Pharmacodynamic Modelling of Pre-existing and Emerging Resistance of Pseudomonas aeruginosa to Colistin
IV-34 *Marta Valle* Effect of Ritonavir Concentrations on Atazanavir Pharmacokinetics: Population Pharmacokinetic Analysis
IV-35 *Georgia Valsami* Assessment of dosage regimens of tigecycline in hospitalised patients
IV-38 *Jan-Stefan van der Walt* The effect of nevirapine-based antiretroviral therapy on the population pharmacokinetics of artemether and dihydroartemesinin in HIV-infected adults
IV-42 *Max von Kleist* A Mathematical Modelling Framework to Assess the Impact of Nevirapine-based Prophylaxis on vertical HIV Transmission
IV-45 *Toshihiro Wajima* Pharmacokinetic/pharmacodynamic Modeling and Long-term Simulation of Dolutegravir (DTG, S/GSK1349572) in Integrase Resistant Patients with a Simple Viral Dynamic Model
IV-54 *Hongmei Xu* Mechanism-based Modelling of the Antagonism between Polymyxin B and Levofloxacin against Pseudomonas aeruginosa using Mono- and Combination Therapy
IV-57 *James Yates* Population PK/PD modelling of AZD9773 in patients with severe sepsis.
IV-62 *Chao Zhang* Population Pharmacokinetics of Lopinavir and Ritonavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-infected Adults
IV-66 *Simbarashe Peter Zvada* Population Pharmacokinetics of Isoniazid in Children with Pulmonary Tuberculosis

Posters: Inflammation

II-24 *Leonid Gibiansky* Mechanistic Modeling of the Link between Interleukin 6 Receptor Blockade with Tocilizumab and Its Hematological Effects
III-1 *Gilbert Koch* Semi-mechanistic modelling of collagen-induced arthritis in mice and of the effect of administration of an anti-Granulocyte Macrophage Colony-Stimulating Factor antibody using delay differential equations
III-55 *Etienne Pigeolet* Population PKPD modeling of dose-response and time course of peripheral lymphocytes after single and repeated administration of the S1P1/5 modulator, BAF312, in healthy volunteers.

IV-61 *Miren Zamacona* Model based approach to inform early clinical development for a biologic

Posters: Model evaluation

I-51 *Emmanuelle Comets* Prediction discrepancies (pd) for evaluation of models with data under limit of quantification
II-33 *Namyi Gu* Population Pharmacokinetics of a new TRPV1 antagonist in healthy volunteers.
II-49 *Masoud Jamei* Modelling the Effect of Interleukin-6, an Inflammatory Cytokine, on Time-dependent Reduction of Cyclosporine Clearance: An Application of the Simcyp Population-based Simulator to Suppression of CYP450 by Biologics
III-7 *Marc Lavielle* Improved diagnostic plots require improved statistical tools. Implementation in MONOLIX 4.0
III-10 *Annabelle Lemenuel-Diot* External evaluation of a Hepatitis C viral kinetic model which links viral dynamics to sustained virologic response (SVR)
III-51 *Klas Petersson* Assessment of bias in model parameter estimates of continuous time Markov models for categorical data

Posters: Oncology

I-6 *Orna Amir* Predictive Model for Identification of Responders/Non Responders in Metastatic Breast Cancer Patients Treated with Docetaxel
I-15 *Brendan Bender* A semi-mechanistic population Pharmacokinetic-Pharmacodynamic (PKPD) model of thrombocytopenia characterizing the effect of trastuzumab-DM1 (T-DM1) on platelet counts in patients with HER2-positive metastatic breast cancer
I-21 *Michael Block* Mechanistic PBPK/PD modeling for prediction of study outcome of cancer therapies: Translating in-vitro information into valid in-vivo predictions
I-23 *Guillaume BONNEFOIS* A nonlinear mixed effect model to study albumin-mediated drug transport into endothelial cells in vitro.
I-24 *Stephan Borghorst* Age Dependent Volume of Distribution of Pegylated Asparaginase (OncasparTM) in children and adults
II-9 *Fernandez Eric* Using the Virtual Tumour to predict and optimize drug combination regimens
II-14 *Gregory Ferl* Population analysis of the DCE-MRI response of liver metastases to a single dose of bevacizumab in CRC patients
II-16 *Nicolas Frances* Integrating distribution to tumor tissue into a dynamic PK/PD model to evaluate the anti-cancer effect of erlotinib in patient-derived LXFA 677 tumor xenograft mice
II-28 *Iztok Grabnar* Bayesian Estimation of Methotrexate Pharmacokinetics in Children with Acute Lymphoblastic Leukaemia and Prediction of Folinic Acid Rescue
II-31 *Joachim Grevel* A physiology-based model predicts pharmacokinetics, target occupancy in the tumour, and HSP70 biomarker response in serum for the HSP90 inhibitor, 17-AAG
II-36 *Neeraj Gupta* Population PK and PK/PD Analysis of Intravenous Investigational Agent MLN9708 in Solid Tumors and Lymphoma Patients
II-52 *Jin Jin* Mechanism-Based Population Pharmacokinetic (PK) Modeling of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449), a Novel Molecule with Unique PK Nonlinearity in Humans
III-4 *Steve Kuan* Population Pharmacokinetic Modeling of Investigational Agent MLN4924 in Cancer Patients
III-14 *Lars Lindbom* Acknowledging informative dropout by simultaneous model fitting of tumor size and dropout data may improve parameter estimates for tumor growth inhibition

models
III-17 *Paolo Magni* A new population PK/PD model to assess the myelotoxicity of candidate drugs in preclinical and in clinical studies
III-21 *Maria Matoses Osborne* Ex Vivo modeling of the apoptotic effects of Vivia009 and its metabolite in patients with Chronic Lymphocytic Leukemia
III-30 *Daniele Morpurgo* Predicting the Gemcitabine efficacy by a stochastic language based model
III-34 *Ronald Niebecker* Importance of study design for estimation of Vmax and Km characterising nonlinear monoclonal antibody clearance
III-37 *Valerie Nock* Leukopenia following triple high-dose chemotherapy and stem cell rescue
III-50 *Kirill Peskov* Systems Modeling of EphB4/ephrinB2 Signaling Pathways
IV-3 *Franziska Schädeli Stark* A semi-mechanistic population pharmacokinetic model for trastuzumab emtansine (T-DM1) antibody-drug conjugate and total antibody in patients with metastatic breast cancer (mBC)
IV-11 *Alexandre Sostelly* Characterization of the interaction between irinotecan, SN-38 and MBLI-87, a new BCRP inhibitor, with a multi-scale semi-mechanistic PKPD model
IV-27 *Mirjam Trame* Busulfan Dosing in Children: Body Weight versus Body Surface Area or Allometric Body Weight Dosing
IV-50 *Mélanie Wilbaux* Population KPD modelling of CA125 and tumor size in patients with ovarian cancer
IV-58 *James Yates* Characterisation of Xenograft Response to Docetaxel by Nonlinear Mixed Effects Modelling
IV-63 *Jianping Zhang* Population Pharmacokinetics of Lapatinib in Cancer Patients

Posters: Other drugs and diseases

I-5 *Claire Ambery* Modelling impact of dropout mechanisms in Chronic Obstructive Pulmonary Disease (COPD)
I-9 *Jacqueline Anderson* Comparative pharmacokinetics of dimethoate poisoning in the minipig and human
I-49 *Adriaan Cleton* Population Pharmacokinetics of a Monoclonal Antibody Tanezumab in Chronic Pelvic Pain Conditions
II-23 *Cecile Gerard* Factors influencing pharmacokinetics of tacrolimus during the early liver post-transplantation period: a population analysis
III-2 *Julia Korell* Modelling red blood cell survival data
III-28 *Dirk Jan Moes* Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients on a calcineurin inhibitor free regimen
III-47 *Mark Penney* Using Mechanistic Modelling of Cyclic Neutropenia to Predict the Effects of a COPD Therapeutic on Systemic Neutrophil Levels
III-48 *Henry Pertinez* Physiologically based, POP-PK modelling of a bone seeking agent in the ovariectomised rat disease model of post menopausal osteoporosis.
IV-5 *Rik Schoemaker* Modelling Ordered Categorical Allergic Rhinitis Scores in an Environmental Exposure Unit Study
IV-40 *Erno van Schaick* PK-PD modelling of bone density and turnover effects of denosumab based on a circular model of bone remodelling
IV-51 *Christian Woloch* Population Pharmacokinetics of Mefloquine and its Major Metabolite in Healthy Volunteers.

Posters: Other topics - Applications

I-41 *Marylore Chenel* Developing an In Vitro – In Vivo Correlation Model Using a Population Approach in NONMEM
I-47 *Jae Yong Chung* Modelling of Atorvastatin Pharmacokinetics in relation to SLCO1B1 genotype and Simulations for Bioequivalence Study
I-57 *Willem de Winter* Dynamics of a Two-Receptor Binding Model: How Affinities and Capacities Translate into Long- and Short-Term Behaviour and Physiological Corollaries
I-59 *Ivan Demin* Longitudinal model-based meta-analysis in rheumatoid arthritis: an application towards model based drug development
I-61 *Vincenzo Luca Di Iorio* Application of Stochastic Differential Equations to Disease Progression in a Neuropathic Pain Model in Rats
II-2 *Anne Dubois* Pharmacokinetic bioequivalence analysis of biologics using nonlinear mixed effects modeling
II-3 *Anne Dubois* Clinical trial simulations to design a crossover study assessing the equivalence on the pharmacodynamic surrogate marker between an immediate and a modified release formulations
II-10 *Charles Ernest* Multinomial Markov-chain model of sleep architecture in Phase-Advanced Subjects (PAS)
II-15 *Martin Fink* Diversity: Academia-Industry Collaborations on Modeling and Simulation to enhance Scientific Capability Development – The Novartis Experience
II-21 *Sathej Gopalakrishnan* Population PK/PD evaluation of the effect of dienogest on Hoogland Score in young healthy women
II-37 *Manish Gupta* Application of Two-Target Quasi-Steady-State (QSS) Model in Population Pharmacokinetic and Pharmacodynamic (PK-PD) Modeling of MNRP1685A in Cynomolgus Monkeys
II-38 *Serge Guzy* Optimizing The Entire Drug Development Process Using Pharmacometric Tools: From Preclinical To Marketing
II-50 *Candice Jamois* Title Pharmacokinetic-Pharmacodynamic Modeling of the Relationship between Aleglitazar Exposure and Lipids Response in Type 2 Diabetes Patients.
II-51 *Hyewon Jeon* A Population Pharmacokinetic/pharmacodynamic Approache of Drug X in Healthy Korean
II-59 *Thomas Kerbusch* Phase 2b dose selection for the treatment of autoimmune disorders leveraging comparator data
III-13 *Lay Ahyoung Lim* Development of a longitudinal model for characterizing adverse events of psychiatric drugs in routine clinical care
III-22 *Hugh McDevitt* Technology Roadmap to Support Model Based Drug Development
III-27 *Enrica Mezzalana* Title: Quantitative Assessment of First Night Effect in a Polysomnographic Insomnia Study through a Multinomial Mixed-Effect Markov-Chain Model
III-31 *Flora Musuamba-Tshinanu* KPD modelling of trough FEV1 in chronic obstructive pulmonary disease (COPD).
III-44 *Zinnia Parra* Target Mediated Drug Disposition Model to Describe the Expression and Kinetics of IL12 And IFNγ in Gene Therapy
III-52 *Olivier Petricoul* From Animal to Human with a new monoclonal antibody: An example of the use of pharmacokinetics only to assist on the choice of first in human dose.
III-57 *Gregory Pinault* A structured approach to industrialize the data sourcing to support model based drug development
III-65 *Martijn Ruppert* Population PK/PD Modeling of a Hepatitis C NS3 Inhibitor
IV-2 *Tarjinder Sahota* Parameterisation of biomarker response in the assessment of long term safety

IV-7 *Yi SoJeong* Population Pharmacokinetics of a Novel Proton Pump Inhibitor, Drug Y, in Healthy Volunteers
IV-13 *Andreas Steingoetter* A population pharmacokinetic model for Gd-DTPA in DCE-MRI
IV-22 *David Ternant* Influence of the FcγRIIIa genetic polymorphism on the effect of antithymocyte globulins on lymphocyte populations in kidney transplantation
IV-26 *Dorota Tomalik-Scharte* Evaluation of Circadian Rhythms in Hepatic CYP3A4 Activity Using Population Pharmacokinetics of Midazolam
IV-32 *Venkata Pavan Kumar Vajjah* Application of pharmacometric principles to quantify the effect of decontamination on the pharmacokinetics, pharmacodynamics and event times of venlafaxine in overdose
IV-49 *Pawel Wiczling* Pharmacokinetics and Pharmacodynamics of Propofol in ASA III Patients Undergoing Abdominal Aortic Surgery
IV-52 *Dan Wright* Development of a Bayesian forecasting method for warfarin dose individualisation
IV-53 *Rujia Xie* Model based meta-analysis (MBMA) to support the development of decision criteria in dental pain studies
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PAGE2011 Oral programme and Software Abstracts

A-05 *Pascal Girard* A Semi-mechanistic Model of Lymphocyte Dynamics in Patients with Multiple Sclerosis Treated with Cladribine Tablets

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Objectives: Cladribine tablets therapy has shown substantial effectiveness in multiple sclerosis (MS) [1–3]. Since the drug selectively reduces peripheral lymphocyte counts, monitoring of absolute lymphocyte count (ALC) is pivotal. According to the Australian Prescribing Information [4], treatment (3.5 mg/kg cumulative dose over 96 weeks) is initiated with 2 consecutive courses of 4–5 days of cladribine tablets at a 28-day interval. Re-treatment comprises 2 additional courses at Weeks 48 and 52. However, patients can not receive a subsequent treatment course when their ALC is grade >=2 (Common Terminology Criteria for Adverse Events), and therefore patients may in rare cases need to delay additional courses while their ALC recovers. We developed an ALC model for MS patients receiving cladribine tablets, to gain more insight into lymphocyte dynamics in such patients by means of clinical trial simulation.

Methods: Our analysis was based on data from the randomized, placebo-controlled CLARITY study, with more than 19,000 ALC measurements from 1319 MS patients receiving cladribine tablets (3.5 mg/kg or 5.25 mg/kg over 96 weeks) or placebo [1]. The exposure–ALC model was developed using NONMEM VI, based on the well-known myelosuppression model [5], adapted to include long-lasting inhibition, and validated by visual predictive check. The exposure–ALC model was implemented in Trial Simulator (Pharsight) to evaluate re-treatment with respect to lymphopenia and proportion of patients taking the (full) treatment courses. Patients' covariates and baseline ALC were resampled from the CLARITY database.

Results: ALC response was well described by a model which included both a transient linear and a long-lasting saturable drug effect, driven by cladribine concentrations and cumulative AUC, respectively. The lymphocyte mean transit time in bone marrow was set to 81h. The dual model correctly predicted the rapid drop and slow recovery of ALC over time. The recovery t1/2 was long (average 90 weeks) and highly variable between patients (138%). Gender was the only covariate identified, women being more sensitive to transient drug effect (+31% in slope).

Conclusion: The dynamics of ALC response to cladribine tablets was quantified and characterized based on a large database in MS. A dual model with transient and long-lasting drug effects described the time-course of ALC well. The proposed model allows prediction of ALC dynamics in patients receiving cladribine tablets in a clinical trial or market setting.

References:

[1] Giovannoni G, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010;362(5):416–26.
[2] Savic R, Munafo A, Karlsson M. The effect of cladribine tablets on disease progression in multiple sclerosis: a non-linear mixed effect analysis. Poster P477 presented at: 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 13–16 October 2010, Gothenburg, Sweden.
[3] Savic R, Munafo A, Karlsson M. Disease progression model for multiple sclerosis and effect of cladribine tablets therapy on clinical endpoints. Poster presented at: American Conference on Pharmacometrics (ACoP), 3–6 April 2011, San Diego, USA.
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Disclosures/Acknowledgements:

This study was funded by Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.
AL. Quartino and MO. Karlsson are paid consultants for Merck Serono S.A.; P. Girard and A. Munafo are employees of Merck Serono S.A.

A-06 *Mats Karlsson* Population Pharmacodynamics of Cladribine Tablets Therapy in Patients with Multiple Sclerosis: Relationship between Magnetic Resonance Imaging and Clinical Outcomes

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Objectives: We previously developed NLME models to characterize the effect of cladribine tablets on clinical outcomes in patients with relapsing-remitting multiple sclerosis.[1-3] These models allow predictions of relapse rate dynamics and disability progression based on an individual's disease activity, baseline characteristics, renal clearance and cladribine dose. Here, we integrate key MRI readouts into models relating cladribine exposure to clinical efficacy, and delineate the poorly-understood relationship between MRI and clinical markers of MS progression.

Methods: Our database included 2-year data from 1319 patients from the CLARITY study, with an additional 287 patients from the placebo arms of two sc interferon beta-1a studies for the Expanded Disability Status Scale (EDSS) model. To examine the relationship between MRI readouts and clinical endpoints, we tested the effect of MRI burden of disease (BOD) on EDSS score and MRI combined unique (CU) lesion count on relapse rate (RR). First, the MRI data were modelled using a count data approach, with MRI time profiles explained by indirect response model and inhibition of kin with cladribine in an exposure-dependent fashion. Then, MRI models were linked with the exposure-clinical endpoints models, where both simultaneous and sequential approaches were tested. Technical challenges included simultaneous modelling of repeated time-to-event and count data (CU-RR model), as well as handling categorical variable (EDSS) using approaches for continuous bound data.

Results: Predictions from a BOD model were linked to EDSS score. The final model consisted of positive relationships with log-transformed BOD and EDSS score at baseline. CU lesions and RR data were fitted simultaneously. In the final model, RR hazard was linearly related to the model-predicted CU lesion count. In both models, the coefficient of the linear relationship was well estimated from the data. The integrated models resulted in a significant model fit improvement and also showed that part of the variability in response was explained by integrated MRI readouts.

Conclusions: Despite major technical challenges and poor mechanistic understanding about MRI-clinical marker relationships, links between MRI lesion dynamics and clinical endpoints were established. The proposed exposure-biomarker-clinical endpoints models integrate a significant amount of knowledge and data, representing a useful platform for quantitative understanding of the MS time course.

Disclosures/Acknowledgements: This study was funded by Merck Serono S.A. - Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany. R. Savic and MO. Karlsson are paid consultants for Merck Serono S.A.; A. Munafo are employees of Merck Serono S.A.

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[1] Giovannoni G, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010;362(5):416-26.
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[3] Disease progression model for multiple sclerosis and effect of cladribine tablets therapy on clinical endpoints. Poster presented at the American Conference on Pharmacometrics (ACoP), 3-6 April 2011, San Diego, USA

A-07 *Bambang Adiwijaya* An integrated, mechanistic model of viral eradication and its clinical applications in treatment regimens with direct-acting antivirals for chronic hepatitis C

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Background: The treatment objective in patients chronically infected with hepatitis C virus (CHC) is a sustained viral response (SVR), which is indicative of viral eradication. In phase 3 studies, a novel combination regimen of a direct-acting antiviral telaprevir (T, an HCV NS3-4A protease inhibitor) and peginterferon-alfa/ribavirin (PR) significantly increased SVR rates in patients with genotype 1 CHC compared with PR alone.

Objectives: To develop a mechanistic model of viral eradication that integrates in vitro potency and resistance data, pharmacokinetics, and viral dynamic response during and after treatment to a combination regimen of telaprevir and PR (TPR) and to apply the model to optimize treatment regimens.

Methods: The model incorporates the presence of HCV variants with differing telaprevir-resistance and fitness, and the diversity in patient responses to PR treatment. The model integrates TPR pharmacokinetics into HCV viral dynamics. The model was developed using in vitro and clinical response data from 28 patients treated with 2 weeks of telaprevir monotherapy [1] and from 478 treatment-naïve CHC treated with either PR or TPR. Model-predicted SVR rates from these studies and from late phase clinical studies were compared with observed data.

Results: The model-predicted SVR rates, generated prospectively, were comparable to the observed rates from 2380 CHC in late-phase clinical trials of regimens with different treatment durations. The model produced consistently predictive results for treatment-naïve. For prior PR-treatment experienced populations, model predictions were generally consistent with the observed SVR rates despite being trained only for treatment-naïve, with more predictive results in prior relapsers than in prior non-responders. The model aided understanding of the novel CHC treatment regimen by integrating resistance and fitness levels, antiviral inhibition by each drug, and patient diversity in IFN-responsiveness, and connected these factors to the ultimate treatment outcome of SVR. The model predicted different eradication times for each HCV variant, which suggested different optimal treatment durations of telaprevir and of PR, which was confirmed in clinical trials.

Conclusion: The proposed model provides a framework to integrate multifaceted mechanistic information and give insight into novel CHC treatment regimens that include direct-acting antiviral agents to optimize treatment strategies.

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A-10 *Nick Holford* A tutorial on time to event analysis for mixed effect modellers

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The connection between PKPD and clinical outcome events can be made using models for time to event. The time of clinical outcome events is understandable in terms of the event hazard, i.e., the rate of occurrence of a time-related event.

The hazard is similar in principle to a drug elimination rate constant. Therefore pharmacokineticists (who are familiar with factors that can describe drug elimination) can easily appreciate how to build hazard models reflecting the influence of drug exposure, disease progression, age, etc. This tutorial will explain how hazard models can be used to describe clinical event times and develop joint models of hazard with commonly used PKPD and disease progression models.

Events may occur a limited number of times in an individual e.g. death happens just once. Other events may occur several times with no obvious limit e.g. epileptic seizures. In each case, events may be observed at an exact time, or may only be known within an interval, or may not be observed at all e.g. due to censoring at the end of a clinical trial. Thus a wide variety of events can be described using the same fundamental concept of the event hazard.

There are strong links between the hazard, the probability distribution of the number of events in a given interval and the probability distribution of the time between events. It is well known for example that a constant hazard can be used to generate count data with a Poisson distribution and times between events with an exponential distribution.

The hazard is usually not constant and is commonly described with a hazard function of explanatory variables such as time or change in disease state. The likelihood of each of these event types can be simply computed from the hazard function and its integral. Joint models of time to event and PKPD can be used in a population context using software such as NONMEM or MONOLIX.

Recommended reading is the book by Collett (1), a key paper by Hu & Sale (2) and a web presentation of the tutorial materials (3).

[1]. Collett D. Modelling survival data in medical research. 2nd ed. Boca Raton: CRC Press; 2003.
[2]. Hu C, Sale ME. A joint model for nonlinear longitudinal data with informative dropout. J Pharmacokinet Pharmacodyn. 2003;30(1):83-103.
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A-12 *Alan Kimber* Parametric time to event methods incorporating time dependent covariates

Alan Kimber
University of Southhampton

Outline: We begin by recapping basic parametric models used in time to event analysis and their properties. Some more flexible parametric models will also be introduced.
Next we consider time dependent covariates and related statistical issues, including the effect of time dependent covariates on quantities such as the survivor function and the hazard function.
We review the extended Cox model that incorporates time dependent covariates, showing why it is easy to use and its potential drawbacks.
We introduce a parametric approach with time dependent covariates and discuss statistical aspects of such an approach and various practical issues.

A-14 *Chuanpu Hu* Informative Dropout and Visual Predictive Check of Exposure-Response Modeling of Ordered Categorical Data

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Objectives: Physician's Global Assessment (PGA) score is a 6-point measure of psoriasis severity (0=cleared and 5=severe). PGA scores were collected from two Phase 3 studies (PHOENIX 1 and PHOENIX 2) of ustekinumab in patients with moderate-to-severe psoriasis [1]. The objective of this study was to develop an exposure-response model for PGA scores and to (1) account for potential dropout influence on model predictions, (2) conduct accurate visual predictive check (VPC) in light of uncertainties in future dosing regimens, and (3) understand the predictive ability of the model.

Methods: A novel joint longitudinal-dropout model was developed. The longitudinal component extended a previous approach using a latent variable semi-mechanistic drug model and placebo effect under the mixed-effect logistic regression framework to model prob(PGA≤k), k=0, 1, ..., by incorporating disease progression. The dropout component extended a previous approach [2] to categorical data, and used the flexible Weibull hazard function. Sequential PK/PD and limited simultaneous estimations were implemented in NONMEM. VPC needs to account for informative dropout. However, simulating dropouts requires the knowledge of future doses beyond the last observation, and assuming the nominal dosing regimen may create biases especially if dose titration is present. A conditional approach, treating the observed data trend as conditional on observed dropouts, was developed to overcome this obstacle. It was then extended to external model validation of the longitudinal component of the joint model. External validation of the dropout component was assessed qualitatively using Kaplan-Meier plots.

Results: 1,995 Patients contributed to 19,340 ustekinumab concentration measurements and 41,668 PGA scores from studies PHOENIX 1 and 2 collected over 2 years, with 373 dropouts. An informative dropout model with Weibull hazard best fitted the data. Conditional VPC results confirmed the differences between the informative dropout model and other models. External validation showed that the prediction errors were small (<3%) in the treatment optimization period but larger (6%) for an extrapolation period.

Conclusions: An informative dropout exposure-response approach was developed to model PGA scores as ordered categorical data. The conditional VPC approach, with no dependence on unknown future dosing regimens, is useful for accurately evaluating informative dropout models and model validation.

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[2] C. Hu and M. Sale, A joint model for nonlinear longitudinal data with informative dropout, Journal of Pharmacokinetics and Pharmacodynamics, 30(1): 83-103, 2003.

A-15 *Marc Gastonguay* Full Covariate Models as an Alternative to Methods Relying on Statistical Significance for Inferences about Covariate Effects: A Review of Methodology and 42 Case Studies.

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Objectives: Covariate (COVT) modeling in population (POP) pharmacokinetics (PK) and pharmacodynamics (PD) has historically been characterized by stepwise hypotheses testing based methods. More recently, a full COVT model (FCM) approach has been proposed for COVT effect inferences in POP PK and PD. The objective of the current work was to perform a systematic review of analyses utilizing the FCM in order to contrast inferences based on statistical significance vs. clinical importance.

Methods: This analysis included the review of 42 case studies of FCM for POP PK (32) or PD (10) analyses, utilizing data from end of Phase 2b or end of Phase 3 development, and conducted within the last 8 years. In all cases, FCM were constructed according to previously described methods [1]. Each analysis included a data reduction step, FCM construction in NONMEM (v. 5, 6 or 7) and determination of 95% CI for parameter estimates (bootstrap or NONMEM asymptotic standard errors). Cases were summarized according to the following characteristics: 1) successful search minimization (MIN), 2) successful covariance matrix of the estimates ($COV), 3) statistical significance of COVT effects, and 4) clinical importance of COVT effects based on magnitude and precision of COVT effect estimates, relative to a clinical effect reference.

Results: Across analyses, the median (MED) number of COVT effects included in the source data was 14 (range 4-60), while the MED number of COVT in each FCM was 6 (range 1-19). 100% of models had successful MIN, and 98% had successful $COV. A total of 258 COVT effects were estimated. 48% of COVT were statistically significant (SS), while 52% were not (NSS). 24% of covariate effects were clinically important (CIMP), 48% were not clinically important (NCIMP), and 28% were insufficiently informed (II). Statistical significance was not a good predictor of clinical importance, where 16% of COVT effects were SS but NCIMP, and 9% of COVT effects were SS but too imprecise to assess clinical importance (e.g. II). Similarly, a lack of statistical significance was not a good indicator of lack of clinically important effect. 20% of COVT effects were NSS, but were not precise enough to rule-out clinical importance (e.g. II).

Conclusions: The FCM method provides for a more useful and accurate inference about COVT effects, when compared to methods based solely on statistical significance procedures.

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A-16 *Celine Laffont* How to analyse multiple ordinal scores in a clinical trial? Multivariate vs. univariate analysis.

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Objectives: Longitudinal measurements of ordinal responses are very frequent in clinical trials to assess drug efficacy and side effects. Usually, several scores are recorded and this multiplicity is an issue for data analysis. Most of the time, each score is analysed separately or an average/aggregated score is used. Both approaches, however, ignore the correlations between scores which very often document different aspects of a same physio-pathological process (e.g. pain, inflammation) and, in the last case, the actual metric of the scores is not taken into account. Very few methods exist to analyse several scores simultaneously [1, 2]. In 2008, Todem et al. proposed a method for the analysis of longitudinal bivariate ordinal data using probit-linear mixed effects models [2]. We propose to generalise their approach and apply it to pharmacokinetic/pharmacodynamic analyses.

Methods: We use the concept of latent variables to derive the joint distribution of K ordinal responses. Each ordinal response Y_k ($k = 1 \ldots K$) is viewed as the categorisation of a continuous, unobserved variable denoted Z_k which is the true variable of interest. We use mixed effects models for the K latent variables, assuming that the random effects for subject i at time t_{ij} (inter- and intra-individual variability) are correlated across scores. Model estimation is performed with a SAEM[3, 4]-like algorithm implemented in C++. The multivariate normal cumulative distribution function is approximated using Gauss-Legendre quadratures. Two simulation studies were carried out with different scenarios to assess the applicability of our method. Drug dose or time-varying drug concentration was used as a covariate in the model. In the end, a principal component analysis was performed to summarise the correlations between scores.

Results: Our method allowed correct estimation of all model parameters, including correlations between scores. As expected, multivariate and univariate analyses gave different results regarding the percentage of subjects within each "crossing" category. In contrast, they produced similar estimation of marginal distributions.

Conclusions: We show that a multivariate analysis can be more appropriate than separate univariate analyses for the assessment of drug efficacy and safety and offers new perspectives in terms of benefit-risk ratio evaluation. The latent variable approach provides a good framework for the modelling of drug effects through various response models.

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A-17 *Julie Bertrand* Some Alternatives to Likelihood ratio and Wald Tests for Pharmacogenetic studies using nonlinear mixed effect models.

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Objectives: Pharmacogenetics can help guiding the dose regimen, however due to the specificity of the genetic covariate methodological improvements are required. Indeed, the Wald and the likelihood ratio tests which are often used to detect a gene effect on a pharmacokinetic parameter using nonlinear mixed effect models (NLMEM) show inflated type I error on small sample size and/or with unevenly distributed genotypes [1, 2]. In this context, we develop and evaluate two alternatives: a permutation test for both statistics and the use of a F-distribution for the Wald test only.

Methods: In the second alternative, four different values are considered for the denominator degrees of freedom (df) i) a denominator df derived from balanced, multilevel one-way analysis of variance (DF_{PB}), ii) a df proposed for NLMEM by Wolfinger (2000), iii) a df adapted for NLMEM from a method developed by Gallant (1975) in multivariate nonlinear models (DF_G) and iv) an extension to NLMEM of the Satterthwaite df formula (DF_{FC}).

All methods are evaluated in terms of type I error and power based on a simulation study as described in [1, 2]. The influence of the estimation algorithm is explored using both FOCE-I in NONMEM 7 and SAEM in MONOLIX 2.1. Also, all methods are applied to the analysis of the pharmacogenetics of indinavir in 40 HIV patients recruited in the COPHAR2-ANRS 111 trial [3].

Results: Using the permutation test, the type I error estimates of the Wald test and the LRT are non-significantly different from the nominal level of 5%, with both algorithms whereas the only method based on an F-distribution that corrects for the type I error inflation of the Wald test is the DF_G method with SAEM. Using the simulation-based correction or the permutation test, the corrected power estimates for the Wald test are much lower using FOCE-I (18.6 and 27.4%) than SAEM (71 and 73%).

In the final model built for the real data, the *CYP 3A4*1B* polymorphism remains associated to the indinavir absorption rate constant whereas the effect of age is discarded based on the p-value estimates from the permutation test and the DF_G approach. The *CYP 3A4*1B* polymorphism was also significantly associated with lower indinavir maximal concentration and decreased short term triglycerids toxicity.

Conclusions: As permutation comes with a substantial computational burden, it should be considered only when decisions based respectively on the asymptotic test and the Gallant alternative are discordant.

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A-18 *Abhishek Gulati* Linking in silico and in vitro experiments to identify and evaluate a biomarker for enoxaparin activity

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Background: Enoxaparin is a low molecular weight heparin (LMWH) anticoagulant and is widely used in thromboprophylaxis for both prevention of primary thrombosis and at higher doses for treatment of patients with pulmonary embolism, deep vein thrombosis and acute coronary syndromes [1-2]. Dosing of enoxaparin, like other anticoagulants, may result in bleeding following excessive doses and clot formation if the dose is too low. For warfarin and unfractionated heparin (UFH), it is usual to measure the time for a blood sample to clot after stimulation with activating agent(s). The standardised tests, prothrombin time (PT), expressed as the international normalised ratio (INR), and the activated partial thromboplastin time (aPTT) assess multiple steps in the clotting system and have been found to provide a good prediction of the risk for bleeding, or clotting and thrombosis, when used with warfarin and UFH respectively [3-4]. Neither the PT nor aPTT produce significant dose-response changes with enoxaparin and so do not provide meaningful evaluation of bleeding or thrombotic risks [5]. Currently there is no multi-step clotting time test for LMWHs such as enoxaparin and assessment of dose effect is seldom performed. Rarely anti-Xa activity is used to assess the dose for enoxaparin, particularly where renal impairment is present, but its utility to predict for clotting or bleeding remains uncertain. We consider there is a need for an alternative, simple, stable, diagnostic clotting time-based test to monitor treatment with enoxaparin.

Aim: The overarching aim of this study was to identify and evaluate plausible activating agent(s) for a clotting time test to assess the anticoagulant effect of enoxaparin. Four specific objectives were identified: (1) *in silico* assessment of standard clotting time tests (aPTT and PT) when applied to enoxaparin, (2) *in silico* identification of new targets for activating a clotting time test, (3) *in vitro* assessment of Xa as a new target for activating a clotting time test and (4) *in silico* predictions of the kinetics of activation in the test. These specific objectives were designed to provide a proof-of-mechanism of the clotting time test where the *in silico* experiments provide the mechanistic framework and the *in vitro* experiments show a realisation of the mechanism.

Methods: (1) A previously developed mathematical model of the coagulation network [6] was used to assess current clotting time tests, PT and aPTT, when applied to enoxaparin. The influences of various initial conditions for the tests were investigated. Effect of enoxaparin was simulated at its therapeutic concentration (taken as 0.5 IU/mL of anti-Xa activity). Time courses of X and Xa in the absence as well as presence of enoxaparin (0.5 IU/mL) were also simulated using the model. (2) The mathematical model was used to identify new targets for monitoring enoxaparin therapy. To identify an activating agent for a clotting time test with enoxaparin, the

in silico clotting system was activated using a range of activated clotting factors or complexes, including: IIa, Va, VIIa, TF, VII-TF, VIIa-TF, VIIIa, IXa, IXaVIIIa, Xa, XaVa, XIa, XIIa, XIIIa, over a range of concentrations, individually and in combination with each other. The aim of the simulations was to identify an activating agent, in the form of a clotting factor, that provides a measurable clotting time (<60 seconds) which was prolonged by at least two-fold in the presence of a therapeutic concentration of enoxaparin (0.5 IU/mL). (3) Xa was identified *in silico* (from method 2) as the best option as an activating agent for a clotting time test to detect enoxaparin effect. *In vitro* experiments were then carried out to demonstrate proof of mechanism of the clotting time test activated by Xa. Clotting times were measured in three different sets of experiments: (i) where the concentration of Xa was varied in the absence of enoxaparin, (ii) where the concentration of Xa was varied in the presence of a therapeutic concentration of enoxaparin (0.5 IU/mL) and (iii) where the concentration of enoxaparin was varied in the presence of a specific Xa concentration. (4) *In silico* assessment of the new target was then used to assess whether the mathematical model supports the findings from the experimental observations on clotting in the presence of varying concentrations of Xa and enoxaparin.

Results: (1) *In silico* assessment of standard clotting time tests (aPTT and PT) when applied to enoxaparin: The simulations suggested that both the PT and aPTT tests used high concentrations of their respective activating agents which result in excessive Xa concentrations that overcome the anticoagulant effect of therapeutic enoxaparin concentration (0.5 IU/mL). Hence therapeutic enoxaparin was predicted to cause only a small prolongation in clotting times in currently manufactured versions of the PT and aPTT. (2) *In silico* identification of new targets for activating a clotting time test: Low concentrations of Xa or tissue factor were identified as plausible activating agents for a clotting time test for enoxaparin. Xa appeared more appropriate as it produced shorter clotting times. (3) *In vitro* assessment of Xa as a new target for activating a clotting time test: A clotting time of 15 seconds, similar to the upper end of the physiological range for the PT was obtained with a Xa concentration of 10 nM and this concentration was used to activate the clotting system to assess the effect of varying enoxaparin concentrations (0.1-1.0 IU/mL). In the presence of 1.0 IU/mL enoxaparin the clotting time was prolonged 10-fold to 153 seconds; in contrast, 0.1 IU/mL enoxaparin caused only a 1.7-fold prolongation to 26 seconds, compared to the control with no enoxaparin. (4) *In silico* predictions of the kinetics of activation in the test: There was good agreement between the *in silico* and *in vitro* results after scaling for Xa concentration.

Conclusions: Using both simulations from the *in silico* model and *in vitro* experiments we show that a Xa clotting time test (we have called this the "XaCT Test") can potentially assess the effect of enoxaparin on the clotting system. The next stage of the development of the prototype "XaCT Test" will be a proof-of-concept study that would validate the novel "XaCT Test" using plasma from wide range of healthy volunteers. A successful proof-of-concept study would mean that this "XaCT Test" could then be evaluated in patients receiving therapeutic LMWH to assess the predictive performance of the XaCT test for reduced risk of thrombotic and bleeding events. We suggest that the XaCT test might provide a missing direct link for dose optimisation of drugs like LMWH and fondaparinux.

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A-19 *Joshua Pink* Pharmacokinetic-pharmacodynamic-pharmacoeconomic analysis of rituximab for follicular lymphoma

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Objectives:

The early determination of economic value has become an important component of the drug development process. Clinical trial simulations based on PKPD models are already used during this process, for such purposes as exploring drug efficacy and safety, optimising trial design for later phases, and considering the effect of different dosing regimens and patient demographics[1]. We look at extending such simulations from merely considering the question of clinical efficacy to considerations of cost-effectiveness.

This is done using a mechanism-based economic modelling approach which incorporates data obtained during phase II clinical studies on the relationships between dose, exposure and response[2]. Specifically, the outputs from population PKPD models are used as the inputs for economic decision analyses, to generate estimates of cost-effectiveness at a much earlier stage than would be possible using convention health economic techniques.

As a proof-of-concept, we describe three case studies of rituximab for the treatment of follicular non-Hodgkin's lymphoma. The first two relate to previously published economic evaluations, to compare simulation- and trial-based estimates. The third forecasts the clinical and economic outcomes of the PACIFICO study, a phase III randomised controlled trial comparing R-FC (rituximab, fludarabine and cyclophosphamide) and R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone) chemotherapies for the treatment of follicular lymphoma[3].

Methods:

We utilised population pharmacokinetic[4] and pharmacodynamic[5] models linking serum rituximab concentration to progression-free survival (PFS), to simulate the effectiveness of rituximab in various clinical contexts. The PK model is a two-compartment linear model, with body surface area and gender as significant covariates[4]. It was based on a phase II study of rituximab in 102 patients with rheumatoid arthritis.

The PD component is an exponential hazard model that links mean rituximab concentration since the last infusion to PFS[5], with the results dependent on the adjuvant chemotherapy. This model was built by fitting data from two studies of rituximab and validated by predicting the results of two additional separate studies. The combined PKPD model was used to generate simulated PFS data for each clinical scenario.

These data served as inputs to economic models of follicular lymphoma, based on National Institute for Health and Clinical Excellence (NICE) appraisals, to assess the cost-effectiveness of rituximab. The first two, of rituximab as maintenance[6] and first-line therapy[7] respectively, directly replicated the economic models from these appraisals (costs, health state utilities etc).

In a further analysis, the results of the ongoing PACIFICO trial were simulated to generate predictions of cost-effectiveness. This case study more closely replicates how this method might be implemented in practice, with the need to estimate costs and clinical effectiveness before phase III trial results are available. We also conduct a value of information analysis, to estimate the value of future research, based on reducing the uncertainty in results.

Results:

Our analyses suggest an acceptable degree of concordance between simulation- and trial-based estimates of cost-effectiveness. For first-line and maintenance therapy, deviations of £2,099 and £1,355 per quality-adjusted life-year (QALY), respectively, from trial-based incremental cost-effectiveness ratio (ICER) estimates of £8,290 and £7,721 per QALY gained would not affect reimbursement decisions.

The probability of these rituximab-containing regimens being cost-effective at £20,000 and £30,000 per QALY thresholds was 1 for both first-line and maintenance therapy in both simulated and trial-based analyses. The range of cost-effectiveness thresholds over which more than 5% of simulations give different results between trial and simulation based analyses is £3,247-£16,256/QALY for maintenance therapy and £6,168-£13,872/QALY for first-line therapy.

Sensitivity analyses, performed to quantify the relative impact of different sources of parameter uncertainty on cost-effectiveness, demonstrated that changes in individual parameters resulted in deviations that were very similar in both trial and simulated methods.

For the PACIFICO case study, the ICER for R-FC versus R-CVP is £19,950/QALY, with an 80% probability of being cost-effective at £30,000/QALY threshold for cost-effectiveness.

Conclusions:

Our analyses demonstrate the feasibility of mechanism-based economic analyses. Trial-based and PKPD-based estimates of cost-effectiveness were concordant, and decision uncertainty (the probability of cost-effectiveness at the payer's threshold) was equivalent. The deviations between simulation- and trial-based estimates of cost-effectiveness are no greater than between analyses based on different clinical trials.

Such an analysis may have utility during drug development in: (i) assessing the effect on cost-effectiveness of considering different sub-groups or dosing schedules; (ii) exploring the impact of protocol deviations; (iii) determining pricing structures, particularly in the context of value-based pricing. A pharmacokinetic-pharmacodynamic-pharmacoeconomic approach has distinct advantages over conventional economic evaluations which are empirical, and generally reliant on the results of phase III trials.

There are limitations to our approach: the results of such an analysis will be inherently uncertain, because of the extensive parameterisation of both the pharmacological and economic models.

However, this uncertainty can be studied using value of information analysis, which quantifies the cost of reducing parameter uncertainty. Early indications of cost-effectiveness can thus be used to direct future research based on these costs, both by informing the design of phase III trials, and indicating important parameters for accurate quantification.

The population PKPD-based approach described here is consistent with Sheiner's "learning and confirming" paradigm for the clinical phases of drug development and consequently might help facilitate a coordinated modelling approach across pharmaceutical industry Research & Development, Pricing & Reimbursement, Health Economic & Outcomes Research, and Strategic Planning sections.

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A-20 *Elodie Plan* Modelling Techniques Handling Dynamic Pain Scores Characteristics

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Objectives

Pain scales defined by the NIH Pain Consortium [1] include the Numeric Rating Scale, also known as Likert Scale. In this 11-point measurement instrument, the lowest score 0 corresponds to no pain and the highest score 10 to the worst possible pain. Non-linear mixed effects modelling has demonstrated high potential to treat data close to their true nature. The main characteristic of scores is interval-constraints, as there are a finite number of ordered categories. Secondly, like many symptoms, they follow a time-course. Finally, a usually overlooked characteristic of frequently assessed scores is serial correlation between observations.

The objectives of this study were to explore pain scores characteristics, as well as to develop platform models and modelling techniques adapted to fit real data.

Methods

1. Clinical trial

Data from the placebo arms of three Phase 3 multi-centre, randomized, double-blind clinical trials were considered. Screened patients were diagnosed with diabetes mellitus and showed symptoms of painful distal diabetic neuropathy. The primary variable was the overall pain intensity self-rated with a Likert scale provided to each subject as part of a diary and completed on a daily basis.

2. Simulation study

100 stochastic simulations were generated with a baseline response ordered categorical model, whose parameter values were derived from a fit to the real data. A second set of 100 simulated datasets included an empirical linear drug effect on the logit of the categorical part, and the design was changed to four parallel dose arms.

2.1. Structural models handling interval-constraints

Simulated data were analysed in NONMEM VI [2] with an ordered categorical model and two alternative models: a truncated generalized Poisson model [3] and a logit-transformed continuous model.

3. Data analysis

Real data were analysed in NONMEM 7 with three competing models: one truncated generalized Poisson model and two logit-transformed continuous models.

3.1. Model components handling time-course

The population mean score time-course can be characterized through λ in the generalized Poisson model or through the logit of IPREDs in the two continuous models. A non-linear decrease attributable to a placebo effect was described with functions restricting scores to remain between 0 and 10.

3.2. Model components handling serial correlation

A Markov process [4, 5] was combined with the generalized Poisson model relaxing the between-observation independence assumption. This discrete-time process consisted of first-order components formulated to inflate the dependence between the present score and the transition magnitude from the preceding score.

Correlated errors [5, 6] were introduced in the first continuous model with an autoregressive time series (AR(1)). It described a continuous-time correlation between two subsequent errors, which exponentially decreased during the time-interval between two observations.

A stochastic process [7, 8] was implemented in the second continuous model with Stochastic Differential Equations (SDEs). Drift from individual model predictions was incorporated in the system as a standard Wiener process, whose variance increases linearly in time.

4. Model diagnostics

Model evaluation was carried out through newly developed simulation-based diagnostics, adapted VPCs [9], and, for continuous models, also through residual-type diagnostics, based on CWRES [10].

Results

1. Clinical trial

A total of 231 neuropathic patients were randomized in placebo arms. They provided 22,492 pain measurements during 18weeks. All possible scores were present in the raw data. The frequency average signified that central scores were more represented than the tail scores.

2. Simulation study

2.1. Structural models handling interval-constraints

The ordered categorical model included twice as many parameters as the two alternative models: a truncated generalized Poisson model and a logit-transformed continuous model. They all adequately fitted the simulated data. Resimulations after estimation produced proportions of scores in agreement with originally simulated distributions. The statistical power to detect a drug effect was high for all models.

3. Data analysis

3.1. Model components handling time-course

The baseline pain score was estimated between 6.1 and 6.2 by the three competing models: one truncated generalized Poisson model and two logit-transformed continuous models. An exponential decay affecting the baseline was evidenced in all models. The characterised maximum placebo effect and its half-life were also similar, around 20% and 30days, respectively. Parameter precision was reasonable for all models.

3.2. Model components handling serial correlation

The Markov process ($\Delta OFV \approx 11{,}000$; df=13) combined with the generalized Poisson inflated probabilities of absolute transition values 0, 1, 2, and 3. The probability of null transitions was modelled with a time-dependency and was 55% at its maximum.

Correlated errors ($\Delta OFV \approx 2{,}000$; df=1) introduced in the first continuous model had a standard deviation of 1.8. Their autocorrelation exponentially decreased with time and was 47% after one day.

The stochastic process ($\Delta OFV \approx 1{,}800$; df=2) implemented in the second continuous model made autocorrelation in residuals disappear and IIVs decrease. The variance of the scaling diffusion term was estimated to 0.038 $score^2$/day on the logit scale.

4. Model diagnostics

Exploration of specific between-score transitions in terms of frequency or time-course was found useful and transferred to the VPC technique. Simulations of individuals were more realistic after introduction of correlation components. Examination of consecutive residuals was used for inspection of the ability of AR(1) and SDEs to handle autocorrelation in residuals.

Conclusions

Truncated generalized Poisson and logit-transformed continuous models are able to handle interval-constraints of Likert scales. Time-course functions of mean scores can be implemented similarly into the models. In this work, three alternative approaches, which are all new in pain modelling, are proposed to address serial correlation between measurements.

All processes could be implemented in NONMEM and the estimation methods FOCE and LAPLACE were found appropriate, as previously shown [11, 12]. The Markov and the SDE models ran in 1h, whereas the AR(1) model took 1month. Therefore, among the two nested continuous models, SDE led to a slightly higher OFV with 1df more than AR(1), but was considerably faster and with no appreciable difference in the simulation-based diagnostics.

Likert pain scores are difficult to model but important clinical endpoints. This work points to three new models handling these, and presents model diagnostics facilitating model inspection and development.

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A-23 *Malcolm Rowland* Physiologically based pharmacokinetics: Advancing the clinical dimension

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For many years a predominantly academic subject, the application of physiologically-based pharmacokinetic modeling (PBPK) is coming of age in drug development and regulation, reflecting significant advances in recent years in the predictability of key PK parameters from a combination of human in vitro data, drug physicochemical information, and the availability of dedicated software platforms and associated data bases. The complexity of the resulting model depends on the intended application. PBPK is now helping to predict the first-in-human PK, and has the facility to be updated in the light of Phase 1 data. Some of the specific advances and contemporary challenges with respect to predicting the quantitative extent of PK-based drug-drug interactions and the impact of age, genetics, disease and formulation are considered. Also considered are the capability in selecting and designing appropriate clinical studies and its implications for resource-sparing and a more holistic view across the pre-clinical/clinical divide are considered.

A-24 *Ashley Strougo* Scaling pharmacokinetics to estimate the "first dose in children": comparing allometric scaling and PBPK

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Introduction: For the estimation of "first dose in children" scaling of the pharmacokinetics (PK) from adults to children is required. Two of the most frequent applied methodologies are physiologically-based pharmacokinetic modeling (PBPK) and allometric scaling in combination with maturation of clearance (CL) for early life. Both methodologies are accepted by regulatory authorities, but it remains unclear if they are interchangeable. This investigation aimed to compare CL predictions when using both methodologies for morphine, paracetamol and various hypothetical drugs with different pharmacokinetic characteristics.

Methods: PK-Sim® was used to create models for more than 100 hypothetical drugs with different PK properties. These pharmacokinetic characteristics were generated by combining different lipophilicities, low, medium and high clearance liver blood flow, liver diffusion and free fractions for compounds being metabolised by either UGT2B7 or UGT1A6/sulfation. Hypothetical drugs with unrealistic PK properties were excluded from the comparisons. The population wrapper in MoBi® was used to scale the PK to both adults and children. The simulated CL in adults was subsequently used to fit a population model using NONMEM 7. Finally, the estimated CL and its respective inter-individual variability were scaled to children using allometry in combination with published maturation functions. In addition, PBPK model predictions for morphine and paracetamol in children were evaluated by comparison with models developed to describe the paediatric PK data.

Results: In children younger than 1-2 years of age, allometry in combination with published maturation functions yields CL predictions that differ up to a factor 5 from PBPK-based predicted clearance. These differences are related not only to the clearance pathways but also to the extraction ratio of the hypothetical drugs. Evaluation of PBPK predictions for morphine and paracetamol showed that the predicted CL ratios were within a factor two-range and that the respective maturation functions were not always in agreement with the liver enzyme(s) activity.

Conclusion: This investigation provides insights into the physiological meaning of the maturation functions indicating that its use in the scaling of the pharmacokinetics of other drugs requires improvement. Until the current methodologies for scaling PK from adults to children have been extensively validated with paediatric clinical data, methodological uncertainty of the predictions should be considered in the risk-benefit assessment of the "first dose in children".

A-26 *Benjamin Ribba* Evaluation of the antitumor effect of PCV chemotherapy on low-grade gliomas patients with a longitudinal tumor growth inhibition model

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Objectives: To develop a tumor growth inhibition model able to describe the evolution of diffuse low-grade gliomas (LGGs) growth dynamics in patients treated with PCV (Procarbazine, Vincristin, CCNU) chemotherapy, and to use this model as a tool to suggest potential improvements of the chemotherapy regimen.

Methods: Model building was performed with longitudinal tumor size (mean tumor diameter) data assessed through imaging techniques in 21 patients representing 254 observations in total [1]. The model was formulated under a population approach as a system of ordinary differential equations distinguishing between two cell populations: one proliferative treatment-sensitive cell population and one quiescent treatment-resistant cell population that spontaneously undergoes apoptosis. Monolix was used to estimate the population and individual parameters.

Results: Consistent with LGGs biology, the model estimated that LGGs consist mostly of quiescent cells. Despite large inter-individual variability the model correctly predicted individual tumor response profiles in the 21 patients. In analyzing evolution over time of proliferative and quiescent cell compartments, the model suggested that in some patients the six-week interval between PCV cycles might be suboptimal and that lengthening the time interval between cycles might improve the duration of response. In the present series, simulating tumor growth responses with time interval between cycles lengthened to 9 months resulted in delaying tumor regrowth after treatment by more than 20 months in the mean, in comparison to the classical 6 weeks PCV regimen.

Conclusions: Based on the hypothesis that LGGs consist of proliferative treatment-sensitive cells and quiescent treatment-resistant cells that spontaneously undergo apoptosis, we propose a

mixed-effect model that accurately describes the evolution of these tumors during and after PCV chemotherapy. This model suggests that tailoring the time interval between PCV cycles according to the individual growth characteristics of LGGs may be a possible means by which to increase the efficacy of this chemotherapy regimen.

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A-27 *Emma Hansson* PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3 and sKIT as Biomarkers of Tumor Response and Overall Survival Following Sunitinib Treatment in GIST

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Objectives: The aim of the present study was to investigate potential biomarker relationships for tumor response and treatment outcome (overall survival) with focus on VEGF, sVEGFR-2, sVEGFR-3, and sKIT following Sutent® (sunitinib) treatment in patients with gastro-intestinal stromal tumors (GIST).

Methods: Data on the four biomarkers, tumor size and survival were available from 303 patients following up to 85 weeks of treatment with sunitinib and/or placebo. The time courses of the biomarkers were characterized by individual parameter estimates obtained from previously developed indirect-response models [1]. Dose, daily AUC and relative change in biomarkers from baseline over time were evaluated to describe the longitudinal tumor size data with a tumor growth inhibition model [2]. Observed tumor size at baseline was incorporated as a covariate acknowledging a residual error in the measurement [3]. A logistic regression model for the time course of dropout was developed where different tumor size measures, time, AUC and progressive disease were evaluated as predictors. A time-to-event model with a hazard function including potential predictors such as tumor size/biomarker levels at baseline and relative change in tumor size/ biomarkers from baseline over time was developed to describe the survival over time.

Results: The predicted time course (relative to baseline) for sKIT described the longitudinal tumor size data statistically significantly better than dose or daily AUC. However, the model improved significantly when AUC and sVEGFR-3 were also added as predictors. Drop out was characterized by length of treatment, tumor size and progressive disease according to the RECIST criteria. The relative change in sVEGFR-3 over time and tumor size at baseline were significant predictors of survival.

Conclusions: The identified relationships between the circulating soluble proteins sKIT, sVEGFR-3 and tumor size and between tumor size, sVEGFR-3, and overall survival indicates a potential use of these biomarkers as early predictors of tumor response and clinical outcome in GIST. sKIT and sVEGFR-3 appear to be on the casual path of GIST and could be hypothesized to be a marker for the inhibitory effect of sunitinib on KIT (a kinase part of the pathogenesis) and for the anti-angiogenic activity.

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A-28 *Ines Paule* Individual Prediction-Based Dose Adaptation Of Capecitabine: In Silico Comparison With The Standard Method, Impact On Limiting Toxicity and On Antitimour Efficacy

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Objectives: Individual prediction-based dose adaptation (IPBDA) method using an ordinal data model of toxicity has been developed for anticancer drug capecitabine-induced hand-and-foot syndrome (HFS) and presented previously [1]. A comparison with the standard dose adaptation by in silico clinical trials was performed and showed the superiority of the IPBDA in terms of toxicity, but did not inform about the impact on antitumor efficacy. When a model of colorectal tumours and capecitabine's effect on them has been published [2], we could extend the previous work by including the efficacy aspects into simulations and dose adaptation decisions. The objective was to find the most advantageous dose adaptation method in terms of grade>=2 HFS reduction without reducing antitumor efficacy by comparison with the standard approach for dose adaptation.

Methods: HFS and tumour models: HFS grade probabilities were described using a mixed-effects proportional odds Markov model [3]. Tumours were described by a mixed-effects model relating the sum of the largest tumour diameters and drug doses [2].
Dose adaptation procedures: The standard method was to reduce the initial dose by 25% after second event with HFS grade>=2 and by 50% after the third one. The IPBDA consisted of: (1) estimating the individual random effects (EBEs of ETAs); (2) choosing the new dose so that the average risk of HFS grade>=2 over the next 3 weeks would be closest (but not higher) to the target risk. Dose reductions could be started after the first occurrence of HFS (even grade 1). Many variations were tested: different target risks, lower and upper limits for dose, conditions for allowing dose increase.
Comparison was made in terms of toxicity related criteria: % of patients having (reoccurring) events with grade>=2 HFS, average number of weeks with grade>=2 HFS, of events with grade >=2 HFS, their duration, % of patients who dropout due to HFS, as well as efficacy related criteria: % of patients having tumour response, % of patients who have progression of disease, relative change from baseline of tumour sizes.

Results: The best results in terms of HFS grade>=2 reduction and equivalent antitumour effect were found with IPBDA where the target risk was 4%, lower dose limit was 50% of the initial dose, dose increases were allowed up to 150% for patients without any HFS starting after 12 weeks or those having grade 1 for at least 6 consecutive weeks. The benefit was on average 10 days less of grade>=2 HFS, by reduced frequency and length of reoccurring events with grade>=2, 7% less of dropouts due to HFS.

Conclusions: IPBDA provided a small but clinically relevant improvement. Dose adaptation based on ordinal data model is limited by poor EBEs [4]. However, in the case of HFS, the main hurdle to reduce toxicity was the insensitivity of response to dose changes.

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A-29 *Coen van Hasselt* Optimizing monitoring strategies of trastuzumab induced cardiotoxicity: Development and application of a population pharmacodynamic model quantifying trastuzumab induced changes in cardiac function

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Introduction

Trastuzumab is a humanized monoclonal antibody that selectively binds to the extracellular domain of HER2, and improves outcome in early and advanced HER2+ breast cancer [*1-3*]. Adjuvant trastuzumab treatment of HER2+ breast cancer consists of 3-weekly dosing during 1 year.
Trastuzumab treatment is associated with cardiac dysfunction mostly manifested by a decline in left ventricular ejection fraction (LVEF) [*4,5*]. Moreover, prior anthracycline therapy increases the risk for cardiac dysfunction[*6*]. Therefore, cardiac function is monitored throughout trastuzumab treatment by repeated measurements of the LVEF. There is substantial uncertainty regarding the optimal clinical management of trastuzumab induced cardiotoxicity, for instance regarding the optimal interval of LVEF monitoring, the optimal time of recovery after cardiac toxicity, and the feasibility of patient-tailored monitoring strategies. In order to answer these clinically important questions it is essential to be able to make quantitative inferences on the sensitivity to, and recovery from trastuzumab-induced cardiotoxicity, the relationship with important determinants such as anthracycline therapy, and the magnitude of between-subject variability.

Objectives

1. To develop a population PD model for trastuzumab induced cardiotoxicity in terms of the LVEF, and to identify potential predictors of inter-patient variability on pharmacodynamic parameters.
2. To develop and apply a simulation framework that simulates the LVEF-time profiles, incorporating treatment interventions, to quantitatively assess optimal cardiac monitoring strategies during adjuvant treatment of HER2+ breast cancer.

Methods

A) Model development

An unselected representative cohort of HER2+ primary and advanced breast cancer patients treated with trastuzumab, with and without prior anthracycline treatment, was included in this analysis. The data analysis was conducted using NONMEM[*7*]. PK was described using dosing

history, together with a previously published PK model[*8*]. For the structural model, different effect compartment models were considered. The L2-method[*9*] in NONMEM was used to simultaneously analyze LVEF values that were partially available as duplicate measurements. Model predictions were evaluated using goodness-of-fit diagnostics and normalized prediction distribution errors (NPDE). Parameter precision was assessed using a non-parametric bootstrap.

B) Simulation framework

Simulation framework development
A simulation framework was developed to quantitatively assess the safety and efficacy of cardiac monitoring protocols during adjuvant trastuzumab treatment. The simulation framework comprised the following steps:

1. Simulate individual LVEF-time profiles using the developed PK/PD model.
2. Apply treatment pausing or termination, according a cardiac monitoring protocol.
3. Calculate outcome measures to assess the performance of the cardiac management protocol.

The outcome measure calculated included dose intensity, deviation from true time of a cardiac event (CE), percentage of patients with a CE, severities of experienced CE's, and specificity/sensitivity and type I/II errors of the screening, where a CE is defined as as a drop in LVEF > 10%, with an absolute LVEF values <50% according to the summary of product characteristics (SPC). Dose intensity was used as the measure for therapeutic efficacy. Currently, the cardiac safety of trastuzumab during adjuvant treatment is assessed according to the monitoring protocol defined in the SPC. Prior to treatment, a baseline LVEF is measured, and consequently the LVEF is monitored at a 3-monthly interval. If a patient experiences a CE, treatment should be paused, and the LVEF should be re-evaluated after 3 weeks. If LVEF has decreased again, treatment is terminated.

Simulation framework application
The following simulation scenarios were evaluated to assess the impact of changing different parts of the current SPC-defined cardiac monitoring protocol:

1. Baseline scenario: Cardiac monitoring protocol in current clinical practice (according to SPC).
2. Optimization of frequency of LVEF monitoring.
3. Feasibility of adaptive monitoring frequency based on patient characteristics.
4. Optimization of time of recovery before re-initiation of trastuzumab.
   The outcome of this simulation study is used to propose optimization opportunities for cardiac monitoring protocols.

Results

A) Model development

A total of 1651 LVEF values from 240 patients were available. The data were best described by an effect-compartment model with recovery, in conjunction with an Emax model.
The population recovery half-life after trastuzumab treatment ($T_{1/2rec}$) was estimated at 49.7 days. A full variance-covariance matrix for between-subject variability (BSV) could be estimated. BSV on $T_{1/2rec}$ and EC_{50} were high, with 79.4 CV% and 103 CV% respectively. The

cumulative anthracycline dose was a significant determinant of the EC_{50}, causing a 45.9% increase in sensitivity (EC_{50}) at the maximum cumulative anthracycline dose. Goodness-of-fit plots, the NPDE, and the bootstrap analysis indicated adequate performance of the model.

B) Simulation framework

The baseline scenario, according to the SPC, indicated that 10% of patients treated prior with the maximum dose of anthracyclines have an expected dosing intensity (DI) of <83%, while patients without prior anthracycline therapy have a higher DI (DI<94% for 5% of patients).
The sensitivity and specificity for detection of a true CE in anthracycline naive patients were 82% and 98% respectively, with a percentage of false-positive LVEF measurements of 54%, and 8% false-negative measurements.
Increasing the monitoring frequency clearly decreases the frequency of extreme absolute values in LVEF (<35%). Moreover, sensitivity increases up to 94% for 1-monthly monitoring, while specificity drops to 91%.
Implementation of adaptive monitoring strategies based on i) the pre-treatment LVEF, ii) the magnitude of LVEF decline at the first 3 months evaluation, and iii) the prior cumulative anthracycline dose, seems to be feasible. The risk of CE's given these three variables was determined. For instance, anthracycline naïve patients with a baseline LVEF of >65%, drop in LVEF at 3 months <13%, have a CE risk of < 0.47%. The risks were also visualized using a response surface.

Conclusion

A population PK-PD model describing the exposure-response relationship for trastuzumab induced cardiotoxicity in a representative patient cohort was developed. The cumulative anthracycline dose was a significant determinant for between-subject variability on EC_{50}. Subsequently, an adaptive simulation-framework was successfully applied to investigate optimal cardiac monitoring strategies.
Further work will focus on prospective validation of optimized monitoring protocols in a clinical study.

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A-31 *Lee Kien Foo* Cost minimization of a phase IIA clinical study

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Objectives:

The purpose of phase IIA studies is to provide initial exploration of drug efficacy and safety in the target patient population. Population pharmacokinetics (PK) of the drug are often explored in phase I studies and point estimates of these parameters (fixed effects, variances of between subject variability (BSV) and residual error) with biomarker information can be used to assist in deciding future dose and dosing regimens. However, since PK parameter values for the patient population may not be the same as for healthy volunteers, a study designed solely on phase I PK may carry a significant risk of failure.

Optimal designs have concentrated mainly on improving the precision of parameter estimates by optimizing the dose and/or sampling schedule. For these designs, the upper boundary of the design space provides the most precise parameter estimates. More recently, designs that include a cost function have been investigated as either a fixed total cost [1] or via different cost functions [2]. In both cases, the cost is determined based on the use of resources and not linked to the success or failure of the study. A decision based on precision only would yield expensive but successful studies whereas a study that considered cost only may be prone to failure. In this project, we propose an approach to determine designs that minimize the expected cost of a clinical study. The expected cost accounts for the probability of success of the study.

Design variables considered here are the number of patients (Np), number of samples per patient (Ns) and their schedule (S), and the defined daily dose (DDD) of the drug. The objective of our study is to locate optimum designs which naturally balances the cost of a clinical study with the probability of study success without setting arbitrary constraints for the design variables.

Methods:

The method will be defined with a specific simulation example. A simple example is chosen for illustration but the proposed method can be generalised to other experiments.

In our example, all patients will receive the same dose, for 3 doses at 24 hours fixed dose interval. Based on prior biomarker data the clinical team has defined a therapeutic window for the 3rd dose to be in the range [0.3unitL^{-1}, 1.3unitL^{-1}]. A clinical study was defined as success if more than 60% of patients have a 3rd dose trough concentration within the therapeutic range.

Expenditure of a clinical study
For a given design (Np, Ns, S and DDD), the expenditure (X) of the study is defined as

X = $[Np x (Cp + Ns(Cs) + Nd(Cd)(DDD))].

Cp is the cost per patient, Cs is cost per sample, Cd is cost per dose and Nd is the number of DDD given. Nd = 3 in our example.

Cost of a clinical study
The total cost T of a successful study was set to the expenditure of the study (X). The total cost T of a failed study was set to the sum of the expenditure of the study (X) plus expenditure to redo a successful study, with an empirical design, ($X^{empirical}$) and the expenditure for the time penalty of having to repeat the study (X^{time}).

In our example, the costs were arbitrarily set to: Cp = $10000, Cd =$10 and Cs will be investigated at $1000, $500 and $100. The empirical design is Np = 70, Ns = 8 and DDD = 1 unit. This design has at least an 80% chance of success if there were no uncertainty in the fixed effect parameters and variance of the random effect parameters, and is used to define $X^{empirical}$. X^{time} is assumed to be either $0 or half of $X^{empirical}$. The proposed method is used to locate a design that minimizes the expected cost, E[T].

Uncertainty in population PK parameters
The uncertainty of a set of population PK parameters was incorporated with an additional level of hierarchy where the parameters are assumed to follow specific hyper-prior distributions. The hyper-parameters were calculated with formulas derived by [3].

Cost optimization
The design variables (Np, Ns, S, DDD) were optimised using an exchange algorithm. At each iteration of the exchange algorithm, the hyper-prior was updated to reflect the information content of the proposed study which was evaluated with POPT [4]. The trough concentration of the 3rd dose was calculated for each patient in the study and random error included. E[T] was determined by Monte-Carlo sampling of 1000 replications of each study design for population PK parameters generated from the hyper-prior distribution, where on each realisation of a study the success or failure and total cost T of the study was evaluated.

Simulation study
The PK model was given by a one compartment first order input and output and a combined error model. The fixed effects estimates were assumed to be multivariate log normal with nominal mean of CL = $0.03Lh^{-1}$, V = 1L and Ka = $1h^{-1}$. The variances of the BSV are assumed to be the same with value 0.1. The proportional and additive errors were assumed to be normal with mean 0 and variance 0.1 and 0.05, respectively.

The nominal means of CL, V and Ka were assumed to follow a normal hyper-prior distribution. The variances of the BSV were assumed to follow an inverse Wishart distribution. The variance of the proportional error was assumed to follow an inverse Gamma distribution.

Results:

In all cases the design that minimized the expected cost did not consist of any design variables being located at the boundary of the design space.

Without time penalty
The optimal design when Cs = $1000 was Np = 33, Ns = 6 and DDD = 3unit. E[T] was

$686,210 providing a power of 88%.
When Cs = $500, the optimal design was Np = 18, Ns = 15 and DDD = 3unit. E[T] was $442,330 with a power of 87%.
When Cs was $100, the optimal design was Np = 14, Ns = 20 and DDD = 3unit. E[T] was $320,880 with a power of 80%.

With time penalty
The optimal design when Cs = $1000 was Np = 56, Ns = 4 and DDD = 3unit. E[T] was $923,450 with a power of 93%.
When Cs = $500, the optimal design was Np = 46, Ns = 7 and DDD = 3unit. E[T] was $653,130 with a power of 98%.
When Cs = $100, the optimal design is Np = 38, Ns = 8 and DDD = 3unit. E[T] was $429,740 with a power of 98%.

Conclusions:

An approach was developed to minimize the cost of a clinical study, where the cost considers both the cost of success and failure. The designs did not reach boundary values of the design space. These designs naturally account for uncertainty in the prior parameter values. Although a secondary outcome, it was interesting to see that (1) including an additional cost penalty for time delays changes the overall study cost and increases patient recruitment, (2) the cost of blood samples (Cs) unless extremely high has limited impact on the design, and (3) all designs tended to favour higher power (80% or more on all cases). Further work with real examples is warranted.

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A-32 *Sebastian Ueckert* Explicit Optimization of Clinical Trials for Statistical Power

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Objectives: Optimal design (OD) theory as a tool to increase the efficiency of clinical studies, though theoretically well-established, still suffers from a low frequency of practical implementation. Among the reasons for this discrepancy is the poor communication of benefits and potential gains, which are mainly based on measures of parameter precision. Statistical power, where applicable, constitutes a more accessible quantity to measure the quality of a design, but its connection with OD has been investigated only in isolated cases [1,2]. In this work we propose an improved statistic more generally applicable and demonstrate the direct optimization of a clinical trial design for statistical power.

Methods: A new statistic derived from the general formulation of the Wald approximation was used to predict the statistical power for given trial designs using different pharmacometric models. The predicted value was compared, together with the classical Wald statistic [1,2], to a type I error-corrected model-based power determined via clinical trial simulations. In a second step, a study design for maximal power was determined by directly maximizing the new statistic. The resulting power-optimal designs and their corresponding performance based on empirical power calculations were compared to designs determined with the D and Ds optimality criteria. All OD related calculations were performed using PopED V2.11 [3], simulation and estimations used PsN V3.3 in connection with NONMEM 7.1.2.

Results: Comparisons of empirically determined power and the newly developed statistic, showed excellent agreement across all models and scenarios investigated. This was in contrast to the classical Wald statistic, which consistently over-predicted the reference power with deviations of up to 90%. Designs maximized using the proposed metric differed from D and Ds optimal designs and showed equal or up to 20% higher power in the subsequent clinical trial simulations. Furthermore, the proposed method was used to minimize the number of individuals required to achieve 80% power through a simultaneous optimization of study size and study design. The targeted power of 80% was confirmed in subsequent simulation studies.

Conclusions: A new statistic was developed, allowing for the explicit optimization of a clinical trial design with respect to statistical power. The method can also facilitate in the communication of the value of optimal design calculations to non-modelers.

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A-33 *Peter Gennemark* Optimal design in population kinetic experiments by set-valued methods

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Objectives: Optimal experimental design is of importance to obtain accurate and precise parameter estimates from sparse data in population kinetic analysis studies. In traditional methods the structure and statistical properties of the model are mostly assumed known, while the parameters are either assumed known (local optimal design), or known to the level of statistical distributions (robust approach). The objective of this work is to describe and evaluate how set-valued methods [1,2] can be applied to solve optimal design problems.

Methods: We use set-valued methods based on interval analysis; all variables and parameters are represented as intervals rather than real numbers. The evaluation of a specific design is based on multiple simulations and set-valued parameter estimations of designs from the search domain. In the parameter estimation, the output for each parameter consists of a range that is consistent with data [3,4].

Results: We propose a heuristic method for optimal experimental design of population pharmacometric experiments based on a set-valued approach. The method is evaluated on several optimal design problems collected from the literature [5]. The method requires no prior information in form of point estimates for the parameters, since the parameters are represented by intervals and can incorporate any level of uncertainty. Notably, no numerical integration is required as in traditional robust optimal design methods. Sampling times and covariates like doses can be represented by intervals, which gives a direct way of optimizing with rigorous sampling/dose intervals that can be useful in clinical practice. General problems with parameter estimation in non-linear models are avoided in set-valued parameter estimation (no distributional assumptions regarding parameters; no model linearization; problems with local minima are avoided). For non-identifiable problems, e.g., with infinitely many solutions, set-valued parameter estimation brackets all solutions, while the traditional maximum likelihood method only outputs one solution.

Conclusions: Main advantages of the proposed method are that no prior point estimates for the parameters are required, the method works on underdetermined problems, and that sampling times and covariates like doses can be represented by intervals.

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A-35 *Leonid Gibiansky* Modeling of Drugs with Target-Mediated Disposition

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Objectives: To introduce Target-Mediated Drug Disposition (TMDD) model, discuss underlying assumptions and model properties, describe TMDD model approximations, discuss specific conditions when each of the approximation should be used, and describe experience-based recommendations on how to develop a robust model that retains all major TMDD features.

Methods: The term TMDD refers to the biological processes and models where drug-target binding significantly influences both pharmacodynamics (PD) and pharmacokinetics (PK). These are typical for the biologic drugs with high specificity to the intended target. The TMDD model describes the processes on the widely different time scales: fast drug-target binding and relatively slow drug distribution and elimination. Given the typical clinically relevant sampling, this model is rarely identifiable thus requiring use of approximations. Various TMDD approximations have been developed. Selection of the appropriate model requires understanding of the biology and assumptions underlying each of the approximations, careful examination of the available data and model diagnostics.

Results: Investigation of the TMDD equations identified distinct phases in the concentration time profiles. The initial fast phase reflects drug-target binding processes. This phase is followed by a slow phase where the drug, target, and drug-target complex are in a slowly changing equilibrium. Several approximations that differ by the underlying assumptions have been developed. The quasi-steady state (QSS) approximation describes the TMDD system where the elimination of the drug-target complex is much slower than the elimination of the free target. In this case, the drug-target complex contributes significantly to the drug kinetics. This model is especially robust if the total target concentration measurements are also available. The QSS approximation was successful in describing PK and PD of monoclonal antibodies that target soluble receptors. When the drug-target complex is eliminated faster than the free target, the QSS equations can be simplified to result in the Michaelis-Menten (MM) approximation. The MM approximation can also be derived assuming irreversible binding and low free receptor concentrations. The MM approximation was shown to describe PK of many monoclonal antibodies that target membrane receptors. For drugs that bind to both soluble and membrane receptors, the QSS approximation of the two-target TMDD equations can be used. Diagnostic plots play an important role in model selection: dose dependence of the model fit or random effects indicates model deficiency. Identifiability of model parameters is another important factor in the TMDD model selection. To be able to provide a reliable description of the data and insights into biology of the system, the approximation should be flexible enough to describe the data but parsimonious to allow precise estimation of all model parameters.

Conclusions: Modeling of drugs with TMDD requires careful examination of the underlying biology, the available data, and model diagnostics to develop the robust model that describes the observed data and is identifiable given the available data.

A-36 *Stefaan Rossenu* Population Pharmacokinetic/Pharmacodynamic Modeling of a New Antithrombotic Drug, The Nanobody® ALX-0081

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Objectives: Nanobodies® are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. ALX-0081 is a bivalent Nanobody drug product, targeting von Willebrand Factor (vWF). The proposed pharmacokinetic (PK) /pharmacodynamic (PD) model aims at characterizing the PK and PD of ALX-0081 after intravenous (IV) and subcutaneous (SC) administration and evaluating the effects of covariates.

Methods: The population pharmacokinetic/pharmacodynamic analysis was performed using NONMEMVII based on PK and PD samples from healthy volunteers and patients receiving ALX-0081 after single and repeated IV or SC administration. The simultaneous modeling of PK (ALX-0081 levels) and PD (vWF levels) was done according to the model proposed by Benincosa *et al*[1] adapted to a 4-compartmental system. The influence of demographic and physiological characteristics on PK and PD parameters was examined and simulations were performed in special populations for potential dose/dosing regimen adjustment.

Results: Plasma concentration-time profiles of ALX-0081 were best described by a one compartment pharmacokinetic model, with a sequential zero/first order input and a parallel second first order absorption after SC administration. The volume of distribution and the elimination clearance of the free drug were estimated at 5.2L and 5.2L.h^{-1}, respectively. The synthesis rate of the PD marker (vWF) is 1.22nmol.L^{-1}.h^{-1} and the baseline level (R_0) was estimated at 52.2nM. The elimination rate and the volume of distribution of the ALX-0081-vWF complex were 0.048h^{-1} (or $t_{1/2}$ = 14.3h) and 2.1L, respectively. Among the covariates evaluated, creatinine clearance, disease status (healthy *vs.* diseased) and bodyweight showed an influence on the PK and/or PD of ALX-0081.

Conclusions: In this study a PK/PD model has been developed to describe the disposition of ALX-0081 and to characterise the decrease in vWF levels (PD effect) after IV and SC administration of ALX-0081 in humans. ALX-0081 has unique PK properties since only drug bound to the target vWF is retained in circulation and excess drug is rapidly eliminated via glomerular filtration. The latter is depending on the renal function of the patient and can markedly affect the exposure in severe renal impaired subjects without changing the corresponding PD effect.

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A-37 *Angelica Quartino* An integrated G-CSF-myelosuppression model characterizing the target mediated disposition of endogenous G-CSF in breast cancer patients following chemotherapy

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Objectives: Granulocyte colony stimulating factor (G-CSF) is the main regulating factor for neutrophils (ANC) and recombinant G-CSF is frequently used as supportive therapy for patients with or at risk of severe chemotherapy-induced neutropenia. The dominating elimination pathway for G-CSF is through binding to its receptor on ANC, however, the dynamics and interplay of endogenous G-CSF with ANC following chemotherapy has not been characterized. Such knowledge will be valuable for optimization of chemotherapy and assist in identification of patients in need of recombinant G-CSF. The aim of this study was to describe the interaction between endogenous G-CSF and ANC following chemotherapy.

Methods: A prospective study was performed which included 49 breast cancer patients receiving adjuvant chemotherapy with three courses of FEC regimen followed by three courses of docetaxel. Endogenous G-CSF and ANC were measured during the first, second and fourth course. In addition, ANC was monitored at predose and at nadir for all courses. In total, 514 G-CSF and 967 ANC measurements were simultaneously analyzed in NONMEM. A model for myelosuppression [1] formed the basis for ANC but the empirical feedback function on ANC production was substituted with functions of G-CSF.

Results: Endogenous G-CSF was well described by a turnover model with zero-order production. The elimination of G-CSF was proportional (4.7 h/(10^9 cells/L)) to ANC in the circulation. A linear non-specific elimination was also significant (0.50 /h). A rapid increase in G-CSF following glucocorticoid treatment was incorporated as an extra release of G-CSF.

Chemotherapy treatment reduced the proliferative ANC precursors. The proliferation rate of ANC was controlled by G-CSF through a feedback mechanism equal to $(G\text{-}CSF_{circ}/G\text{-}CSF_0)^{\gamma}$. An additional feedback mechanism, where increased G-CSF levels reduced the mean maturation time, resulted in an OFV drop of 115. Model parameters were in line with previous estimates for these treatments [2].

Visual predictive checks showed that the final model captured both the initial rise in endogenous G-CSF following chemotherapy-induced neutropenia and the parallel return to baseline for both G-CSF and ANC.

Conclusions: The integrated G-CSF-myelosuppression model characterized the target-mediated disposition of endogenous G-CSF following chemotherapy and confirms the self-regulatory properties of the system. The model may be a useful tool in further characterization of the system and in schedule optimization of chemotherapy treatment.

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A-41 *Stephan Schmidt* Coping with Time Scales in Disease Systems Analysis: Application to Bone Remodelling

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Objectives: Models characterizing the dynamic behaviour of disease systems as well as the impact of therapeutic interventions can be established at different levels of complexity, ranging from data driven and descriptive to complex mechanistic approaches [1]. While descriptive models may not be predictive beyond the data on which they were established, complex mechanistic approaches may face problems with parameter identifiability. To overcome this limitation, mechanism-based models capturing a system's behaviour rather than its complexity can be established using mathematical model reduction approaches. The aim of this study was to demonstrate the value of mathematical model reduction for characterizing complex dynamical systems using bone remodelling as an example.

Methods: The mechanistic bone cell interaction model proposed by Lemaire et al. [2] was mathematically reduced from a three-dimensional to a two-dimensional system. The dynamic properties of both the full Lemaire model and the reduced Lemaire model were then compared using simulations. In these simulations, the response of both models to changes in the underlying physiology and to therapeutic interventions was evaluated using four physiologically meaningful scenarios: 1) estrogen deficiency/estrogen replacement therapy, 2) Vitamin D deficiency, 3) ageing and 4) chronic glucocorticoid treatment/cessation of glucocorticoid treatment.

Results: On the time scale of disease progression and therapeutic intervention, the full and the mathematically reduced Lemaire model showed negligible differences in their dynamic properties. Both models were suitable for characterizing the impact of changes in the underlying physiology and/or therapeutic interventions on bone forming/resorbing cells for all four scenarios. Reduction to a two-dimensional system yielded new qualitative insight, such as the difference in times scales involved in the onset and washout of treatment effects, and brought down the number of parameters to be identified.

Conclusions: Mathematical model reduction is a valuable approach for analyzing disease systems and simplifying complex models while maintaining their dynamic properties. A significant decrease in the number of parameters to be identified and estimated in addition to an increased system transparency qualifies reduced models as tools to evaluate the impact of

changes in physiological states and/or therapeutic interventions with respect to the different time scales involved.

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A-42 *Elba Romero* Coupling complex mechanistic PK/PD modelling with dynamic system analysis to obtain relevant clinical/biological insights. Application to gonadotropin hormone release agonist

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Objectives: The gonadotropin hormone release agonist triptorelin (TPT) administered subcutaneously or intramuscularly in sustained release (SR) formulations is being used in the treatment of prostate cancer. So far the relationships between plasma drug concentration (CTPT) and response independent of the type of SR, and between a marker of drug exposure and castration [testosterone (TST) levels in plasma < 0.5 ng/mL] have not been established yet. The aim of this study was (i) To develop a predictive receptor-based pharmacokinetic/pharmacodynamic (PK/PD) model for the TST effects of triptorelin. (ii) To extract relevant clinical PK properties of the SR formulations through a formal mathematical analysis of the model.

Methods: Data (CTPT and TST) from a population of 74 prostate cancer patients and 8 healthy volunteers from four clinical trials (one phase I, two phase II, and one phase III) in which five different triptorelin formulations were tested, were analyzed in the current evaluation. Triptorelin was administered by subcutaneous or intramuscular route. PK/PD model development was done by sequential analysis using nonlinear mixed effects (NONMEM VII). Values below the limit of quantification (representing > 50% of TST observations in some trials) were also considered during the analyses and were handled using the M3 method[1]. The dynamic system analysis was done by phase diagrams[2] to explore qualitative changes in receptor dynamics of total receptors and calculate a concentration threshold (CTHD) required to maintain the patient under the castration level .

Results: The PK/PD model developed reflected the agonist nature of triptorelin, the competitive interaction with the endogenous agonist, and the main characteristics of the receptor system: down-regulation and positive feed-back mechanisms. CTHD was calculated as 0.0351 ng/mL; additionally, the system analysis identified a qualitative change in the behaviour of the receptor dynamics at CTPT of 0.044 ng/mL, and represents the inability of the system to achieve levels of TST lower than 0.061 ng/mL beyond that CTPT value .

Conclusions: This work shows the advantage of using system analysis to extract relevant clinical/biological properties in the case of complex PK/PD models, otherwise difficult to confirm with the only use of standard simulation approaches.

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A-43 *Wojciech Krzyzanski* Solving Delay Differential Equations in S-ADAPT by Method of Steps

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Objectives: S-ADAPT is a version of ADAPT II that contains additional simulation and optimization abilities such as parametric population analysis [1]. S-ADAPT utilizes LSODA to solve ordinary differential equations (ODEs), an algorithm designed for large dimension non-stiff and stiff problems. However, S-ADAPT does not have a solver for delay differential equations (DDEs). Our objective was to implement in S-ADAPT a DDE solver using the methods of steps.

Methods: The method of steps allows one to solve virtually any DDE system by transforming it to an ODE system [2]. Fortran subroutines were added to the source S-ADAPT files which enabled it to solve DDE systems with multiple delay times and constant conditions for the past. The S-ADAPT DDE solver utilizes LSODA to obtain the solution. The solver was validated for systems of linear DDEs with one and two delay times and bolus inputs for which explicit analytic solutions were derived. Solving of nonlinear DDE problems were validated by comparing the solutions with ones obtained by the MATLAB DDE solver dde23 [3]. The target mediated drug disposition PK and lifespan based indirect response PD models developed previously for recombinant human erythropoietin (rHuEPO) were used for tests [4]. The performance of S-ADAPT for stiff problems was tested by increasing the erythropoietin receptor binding constant kon to values where the stiffness of the PK/PD model was anticipated.

Results: The user provided subroutines defining DDE problems for S-ADAPT resemble those for ODE problems with an addition of variables for delayed state variables. All necessary Fortran subroutines and global variables are stored in two files that need to be added to S-ADAPT directory. No re-installation is necessary. The comparison of S-ADAPT generated solutions for DDE problems with the explicit solutions as well as MATLAB produced solutions agreed up to number of significant digits set for LSODA by the constants RTOL and ATOL. The DDE solver was capable of solving the stiff PK/PD model with kon = 0.01, 0.1, 1, and 10 1/nM/h, the values that are up to 1000-fold larger than its estimate.

Conclusions: S-ADAPT is the first program designed for population PK/PD analysis that is capable of solving arbitrary DDE models with typical PK input consisting of multiple bolus injections and infusions. The performance of the S-ADAPT DDE solver is identical with the performance of the LSODA for large dimension systems by the virtue of the method of steps.

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A-44 *S. Y. Amy Cheung* Structural identifiability of parallel pharmacokinetic experiments as constrained systems

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Objectives: Pharmacokinetic analysis using compartmental models can be restricted with respect to the estimation of parameter values. This is because the experimenter is only able to apply inputs and observations in a very small number of compartments in the system. This has implications for the structural identifiability [1] of such systems and consequently limits the complexity and mechanistic relevance of the models that may be applied to such experiments. A number of strategies are presented whereby models are rendered globally identifiable by considering a series of experiments in parallel [2].

Methods: Structural identifiability is the property of whether an experiment can uniquely identify the unconstrained model parameters. The ‘same' experiment may sometimes be carried out several times on a system, in which it can be assumed *a priori* that some, but not all, of its rate constants change between experiments. The models representing each experimental observation thus share some common rate constant values depend on the dosing method and physiological nature of the model. This forms a much more constrained structure, encapsulates more information of the system and still can be readily analysed.

Results: The methodology is applied to a number of examples, including classic compartmental models and a series of mechanistic compartmental models such as parent-metabolite models [3]. It is shown that by considering parallel experimental strategies, individually unidentifiable or locally identifiable models, in many cases are rendered uniquely identifiable.

Conclusions: A formulation has been presented that places the concept of parallel experiments in the context of a single constrained model structure. Incorporation of prior knowledge into parallel experiment model structures with constrained parameterization allows sufficient information to be present in the input-output behaviour to give unique parameter estimates. The results show that the parallel experiment strategy can be very powerful in providing a globally uniquely identifiable model.

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S-01 *Kajsa Harling* Perl speaks NONMEM (PsN) and Xpose

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PsN is a toolbox for population PK/PD model building using NONMEM 6 and 7. It has a broad functionality ranging from results extraction from output files, data file sub setting and resampling, to advanced computer-intensive statistical methods and NONMEM job handling in large distributed computing systems. PsN includes stand-alone tools for the end-user as well as development libraries for method developers. New features include covariate model building functionality utilizing the cross-validation, linearization and lasso methods. The existing stepwise covariate model building tool has also undergone a major revision for increased flexibility and stability. In addition, handling of dropout censoring and missing observations in visual predictive checks and a new tool for Monte-Carlo mapped power have been implemented.

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.

The cooperative functionality included in PsN and Xpose permits a synergistic use of both, allowing the end user to easily compute and display various predictive checks and other diagnostics.

Both Xpose and PsN are freely available at http://xpose.sourceforge.net and http://psn.sourceforge.net respectively.

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S-02 *Joakim Nyberg* PopED - An optimal experimental design software

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PopED is an Optimal Experimental Design tool for Non-Linear Mixed Effect Models [1]. Key features of PopED include the ability to optimize over multiple possible models as well as to assume distributions around model parameter values (ED-optimal design). For the latter PopED can use asymptotically exact Monte-Carlo methods or faster performing Laplace approximations for the integration step. PopED allows the user to optimize over any design variable (sample times, doses, number of individuals, start and stop time of experiments, infusion lengths, etc...) greatly enhancing the information content of experiments. Furthermore, PopED can optimize using penalty functions allowing for power optimization, cost optimization, optimization of discrete type data, time-to-event models etc. In addition, the computations can be executed in parallel using Open MPI [2] or Matlab Parallel Compiler Toolbox [3].

PopED consists of two parts, a script version, responsible for all optimal design calculations, and a Graphical User Interface (GUI), facilitating the setup of an optimization task for users. The script version can use either Matlab [3] or Freemat [4] (a free alternative to Matlab) as an underlying engine. The GUI is a window based application written in C# that can be run with .NET 2.0 (MS Windows) or with Mono (Linux/MacOS). In addition to easing the implementation of an experimental design optimization, the GUI also provides model templates, examples, tools for interpretation of the optimal design outcome and ways to validate and simulate models prior to optimization. All these tools are also accessible via the script version of PopED. PopED is freely available at poped.sf.net.

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S-03 *Coen van Hasselt* Piraña: The flexible modeling environment for NONMEM

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Introduction
Piraña is a modeling environment for NONMEM and PsN, and provides an easy-to-use toolkit for both novice and advanced modelers. It can be used for modeling on a local system or on computer clusters. Piraña can be used to run, manage and edit models, interpret output, and manage NONMEM installations. It is easily extendible with custom scripts, and integrates smoothly with R, Xpose4, Excel and other software. Piraña fully supports NONMEM version 7.2 and runs on Windows, Linux and Mac OSX.

Model management

- Logbook-like interface for model management
  Add descriptions, notes, and coloring to models and results. Choose between condensed / detailed model information, and list / tree views.
- Create and edit models
  Create new models from wizard and templates, duplicate model with updated run- and table numbers and parameter estimates. Delete model files and all associated results and table files.

Results management

- Create HTML / LaTeX run reports
  Quickly create formatted reports for a run, containing basic model specifications and estimations results for all estimation methods that were used, including parameter estimates, uncertainty, shrinkage etc. Piraña is compatible with output from NONMEM version 5, 6 , 7.2.
- Extend Piraña with custom scripts
  Custom R-scripts can be used conveniently from within Piraña and run on a specific model, e.g. to automate creation of goodness-of-fit plots. The output image / PDF / html-file can be loaded automatically. Multiple useful scripts are already included with Piraña, which can be customized.
- Built-in Data Inspector
  Allows detailed investigation of e.g. goodness-of-fit plots, or plots of covariates against individual parameter estimates.
- Overview of datasets, output, Xpose files, R scripts
  Quickly open, edit data files and Xpose datasets with a spreadsheet, code editor or in R. Make notes to datasets.
- Convert NONMEM table files to CSV format and vice-versa.

- Convert $DES code to Berkeley Madonna or R-deSolve code for simulation purposes.
- Multiple other functionalityincluded

NONMEM

- Install and manage local / cluster NONMEM installations
  Install NONMEM 5, 6, or 7 from Piraña, or add existing installation to be used in Piraña. Manage and view SIZES variables for NM6 and NM7 installations.
- Run a selected model in the current folder or in a separate folder. Conveniently choose the desired NONMEM installation from a list.
- Follow NONMEM run progression
  Piraña reads intermediate NONMEM output and provides numerical and graphical view of parameters and gradients

PsN

- Start model execution using the PsN dialog
  All PsN commands can be used from a dialog window. The NONMEM version used by PsN for the command can be chosen from a list. The actual command line that is used is displayed and can be edited. The dialog also shows all PsN information for the specific command.
- Special functionality for scm: create configuration file using wizard, select scm file from run dialog.
- Support for PsN run record syntax

Cluster support

- Wizards for creation of configuration files for parallel computation features of NM7.2.
- Connect to computer clusters through SSH
  Computer clusters running NONMEM can be accessed directly through SSH, both from/to Linux and Windows systems.
- Piraña can be installed on the cluster server, and run by multiple clients through SSH-X-window tunneling.

Software

Piraña is written in Perl/Tk and released under a Create Commons license for academic use, and a commercial license. Supported operating systems include Windows, Linux, and Mac OSX. The current version is 2.4.0, which can be downloaded from http://www.pirana-software.com/.

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S-04 *Stephane Vellay* Pipeline Pilot - Data Integration, Analysis, and Reporting Platform

Stephane Vellay, Guillaume Paillard, Eddy Vande Water, Richard Compton
Accelrys

Workflow technology is being increasingly applied in research and development information to organise and analyse data. **Pipeline Pilot** is a scientifically intelligent implementation of a workflow technology known as data pipelining. It allows scientists to construct and execute workflows using components that encapsulate many algorithms. This flexible visual programming language captures and deploys your best-practice processes.

1. **Gather Data**
   - Search, summarise & share your data from multiple disparate sources, Databases or Files, using In-House format checking rules
   - Join together applications within a variety of areas, such as chemistry, bioinformatics, image analysis, high throughput screening, and laboratory data management
   - Features related to security, scalability, database integration, and distributed computing make it an ideal solution for enterprise use
2. **Automate Analysis**
   - Pipeline Pilot allows you to integrate your existing computational resources within a single work environment: NONMEM, WinBUGS, Monolix, Xpose, WinNonlin, PsN, MC Sim, etc.
   - Use standard scripting environments for rapid development of new components: R, MATLAB, SAS, Java, ORACLE, etc.
   - Automate workflows to schedule jobs, then log & archive associated data and reports
3. **Share Results**
   - Automate the creation of standardised reports in various formats: HTML, PDF, PowerPoint, Word, Excel, etc.
   - Present analysis results in a more accessible way, using interactive charts and forms with easy-to-use reporting tools or by integrating third party applications reporting tools
   - Extend Pipeline Pilot protocols throughout your organisation via Web Portals like SharePoint, giving non-expert users access to previously constructed workflows

Come to the free introductory course on Tuesday 7th June, or visit our booth at PAGE 2011 for a demonstration of Pipeline Pilot and web-based solutions developed with it.

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bibliographic web-based tool for PubMed. Infect Disord Drug Targets. 2009 Jun;9(3):366-74. PubMed
[3] Learn more about Pipeline Pilot
[4] Accelrys Community Forums

S-05 *Marc Lavielle* Analysing population PK/PD data with MONOLIX 4.0

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MONOLIX performs maximum likelihood estimation in nonlinear mixed effects models without linearization. The algorithms used in MONOLIX combine the SAEM (stochastic approximation version of EM) algorithm with MCMC (Markov Chain Monte Carlo) and a Simulated Annealing procedure. The convergence of this algorithm and its good statistical properties have been proven and published in the best statistical journals [1,2]. The algorithm is fast and efficient in practice. MONOLIX 3.2 already propose many important and useful features:

- MLXTRAN allows writing complex models (ODEs defined models, count data and categorical data models, time-to-events data models, complex administrations, multiple compartments, transit compartment...)
- An extensive library of PK model (1, 2 and 3 cpts ; effect compartment ; bolus, infusion, oral0 and oral1 absorption ; linear and nonlinear elimination ; single dose, multiple doses and steady state)
- An extensive library of PD models
- Continuous and categorical covariate models,
- Constant, proportional, combined and exponential error models,
- Predifined distributions for the individual parameters (normal, log-normal, logit-normal, probit-normal, power-normal, ...)
- Model selection: information criteria (AIC, BIC), statistical tests (LRT, Wald test)
- Data in NONMEM format,
- Enhanced goodness of fit plots (VPC, weighted residuals, NPDE, ...),
- Mixture models & model mixtures (parameter mixture, between subject model mixture, within subject model mixture),
- Data simulation,
- Automatic reporting,

A beta version of release 4.0 will be presented during PAGE 2011. This version will contain several new important features such as:

- A new MLXTRAN for easy full project programming (any GUI feature can be controlled via MLXTRAN and vice-versa)
- Advanced workflow support (multi-instances & multi-users, GUI-less batch mode)
- PERL scripting (Mass processing, Multi-threaded batch scripts)
- Advanced graphics (stratify the data, interactive plots, create and save custom settings)

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