T-001

Prospectively Applied Quantitative Translational Analysis to Optimize the Clinical Development of PF-06751979: A β-site Amyloid Precursor Protein Cleaving Enzyme (BACE) Inhibitor

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OBJECTIVES: PF-06751979 is a small molecule, selective BACE inhibitor in development for the treatment of Alzheimer’s disease (AD). An exposure response (E-R) model that characterized PF-06751979 pharmacology in mice was subsequently humanized using a combination of model-based meta-analysis (MBMA), systems pharmacokinetic model and human in vitro assays. The humanized model was prospectively applied to optimize the design of a multiple ascending dose (MAD) study to enable early declaration of proof of mechanism (POM).

METHODS: An indirect E-R model was first developed based on the time course PF-06751979 plasma concentrations and cerebrospinal fluid (CSF) amyloid-β (Aβ) levels (the mechanistic biomarker) following a single dose as well as after 5 days of daily dosing in mice. Both the system specific parameters and drug specific parameters from the mouse model were subsequently translated to the human model (Figure 1). More specifically, a MBMA based on multiple compounds that have demonstrated CSF Aβ modulation in the clinic was used to translate maximum Aβ lowering effect (Emax) and CSF Aβ turnover rate in human. A systems pharmacokinetic model based on species-specific expression levels of efflux transporters (which affects PF-06751979 distribution into the brain) was used to project the target site drug concentration in human. Human in vitro assays were used to translate EC50 into the clinic. The humanized model-based simulation was used to design the MAD study, where CSF Aβ concentration was measured at the beginning of the study and at 24 hours post the last dose to verify the target engagement.
RESULTS: The MBMA suggests unchanged Emax and 15-fold slower CSF Aβ turnover rate in human. The systems pharmacokinetic model suggests PF-06751979 brain penetration increases approximately three-fold in human. Integration of these predictions in the humanized model predicts sustained CSF Aβ reduction at around 64% after 14 days of 50 mg QD dosing, which enabled an efficient biomarker sampling scheme for the MAD study to verify POM. This prediction was confirmed by the clinical study result, where CSF Aβ was reduced by 62% at the end of the MAD study.

CONCLUSIONS: The translational analysis quantified pharmacology difference involved in BACE pathway across species and accurately predicted the clinical responses upon inhibiting BACE with PF-06751979. This analysis enabled an efficient and informative MAD study design that provided early confirmation of target engagement.

T-002

A tumor growth inhibition-overall survival model for atezolizumab in first-line non-small cell lung cancer based on IMpower150 study

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Objectives: To develop a multivariate tumor growth inhibition-overall survival (TGI-OS) model in first-line non-small cell lung cancer (NSCLC) patients based on the atezolizumab study (IMpower150 study) [1].

Methods: IMpower150 was a Phase 3 study where NSCLC patients were randomized to receive atezolizumab plus carboplatin plus paclitaxel (Atezo + CP), Atezo plus bevacizumab plus CP (Atezo + Bev + CP) or Bev + CP. Atezo + Bev + CP significantly improved progression free survival and OS compared to the control treatment (Bev + CP). On-treatment tumor growth rate constant (KG) was estimated using time profiles of sum of longest diameters (SLD, RECIST 1.1) and a bi-exponential model [2] implemented in NONMEM version 7.3.0 [3]. A multivariate parametric model linking baseline patient characteristics and KG estimates to OS, was developed as previously described [3]. The model was evaluated in simulating OS distribution and week 4 landmark hazard -ratio (HR) of Atezo treatment combinations vs. control.
**Results:** Out of 1202 patients enrolled, 1106 (92%) were TGI evaluable (at least one post-baseline tumor assessment) and typical SLD profiles showed stronger growth inhibition (benefit) for Atezo + Bev + CP (377 patients) compared to Atezo + CP (360 patients) and to Bev + CP (control, 369 patients) (Figure 1) with tumor doubling times (ln2/KG) of 100, 78, and 61 weeks, respectively.

Figure 1. Typical TGI profiles in the three arms of the atezolizumab IMpower150 study

The final lognormal multivariate TGI-OS model included independent effects of baseline albumin, ECOG performance status, lactate dehydrogenase, number of metastatic sites, Asian race and log(KG). The observed Kaplan-Meier distributions for each of the 3 treatment arms were within the 95% prediction intervals (PI) from the model as well as week 4 landmark HR: 0.84 observed vs. 0.86 (0.72-1.00) predicted (PI) for Atezo + CP vs. Bev + CP and 0.69 observed vs. 0.69 (0.57-0.84) predicted for Atezo + Bev + CP vs. Bev + CP.

**Conclusions:** Atezolizumab OS benefit in combination in first-line NSCLC patients is driven by the decrease in tumor growth rate in atezolizumab treated patients as previously observed in second-line plus patients treated with atezolizumab single agent compared to chemotherapy [3]. This is the first TGI-OS model for a 3-arm immunotherapy combination trial.


**T-003**

Advancing the design of combination drug regimens through integrated PKPD modeling and simulation to improve GBM chemotherapy

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**Affiliation:** ¹Department of Pharmacy Practice (Clinical Pharmaceutical Sciences), College of Pharmacy, Purdue University, ²Department of Pediatrics, School of Medicine, Indiana University, ³Division of Clinical Pharmacology, Department of Medicine, School of Medicine, Indiana University
**Background:** Despite advancements in therapies, such as surgery, irradiation (IR) and chemotherapy, the outcome for patients suffering from glioblastoma remains fatal: the median survival rate is only about 15 months. Even with novel therapeutic targets, networks and signaling pathways being discovered, monotherapy with such agents targeting such pathways has been disappointing in clinical trials. Poor prognosis for GBM can be attributed to several factors, including failure of drugs to cross the blood-brain-barrier (BBB), tumor heterogeneity, metastasis and angiogenesis. Development of tumor resistance, particularly to temozolomide (TMZ), creates a substantial clinical challenge.

**Hypothesis:** Use a biomarker-informed, PKPD-enabled approach to identify combination drug regimens that mitigate resistance development.

**Objective:** Combine TMZ with small molecule inhibitors, currently in clinical trials or approved drugs for other cancer types, and which target GBM at various resistance-signaling pathways induced in response to TMZ monotherapy. Integrate biomarker dynamics into PKPD models to inform the temporal aspects of combination regimen design.

**Methods:** Our initial work is largely based on Cardilin, et al, 2018 that first defines a PK model for each drug, and then links it to a PD model of tumor growth in the presence of a single agent or combinations of drugs. Tumor static concentration (TSC) curves identify exposures of two or three drug combinations predicted to arrest tumor growth. Mice bearing GBM xenograft flank tumors were administered TMZ in combination with several small molecule agents that target TMZ resistance pathways: Abemaciclib (a dual CDK4/6 small molecule inhibitor), RG7388, an MDM2 inhibitor, and GDC0068, an AKT inhibitor. Tumor growth in vehicle treated animals served as the control.

**Results and Discussion:** Combination regimens administered in parallel suppressed tumor growth longer compared to TMZ monotherapy. PK parameters for each drug, and PD parameters quantifying tumor volume dynamics in control and drug treated groups were precisely estimated (coefficient of variation < 30%). Plasma concentrations of TMZ and small molecule inhibitors predicted to arrest tumor growth, as monotherapy or in combination, were determined. The models were used to simulate the time courses for TMZ-sensitive and TMZ-resistant tumor growth for each regimen.

**Conclusion:** Developed models will be presented and used in future studies to define combination doses that will include biomarker measurements indicative of resistance development, and ultimately drive biomarker-informed sequential combination regimen design to test the hypothesis.

**Reference:**

**T-004**

**Population Pharmacokinetic Model of Oxfendazole and Metabolites in Healthy Adults Following Single Ascending Doses**

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**Objectives:** Oxfendazole, a potent broad-spectrum anthelmintic approved for use in cattle, is under translation to human clinical application, targeting human neurocysticercosis and soil-transmitted helminthiasis. This study aims to develop a population pharmacokinetic model for oxfendazole and its two metabolites, oxfendazole sulfone and fenbendazole, in healthy adult volunteers in the first-in-human single ascending doses clinical trial (ClinicalTrials.gov Identifier: NCT02234570).

**Methods:** Following a single ascending oral doses of oxfendazole from 0.5 to 60 mg/kg, plasma samples were collected over a period of 15 days. For the structural model, one- and two-compartment models were tested for oxfendazole in plasma. Model development also evaluated the significance of pre-systemic metabolism in the formation of the major metabolite, oxfendazole sulfone. Other components of the structural model included a depot compartment with less than dose proportional bioavailability and first-order absorption rate constant, and one compartment for each metabolite in plasma. All metabolic rate constants and elimination rate constants are first-order. Model development was performed using non-linear mixed-effect modeling in NONMEM 7.4.2 with ADVAN13 subroutine. Parameters were estimated using first-order conditional estimation method with interaction (FOCE INTER). For concentrations below the quantification limit (BQL), two strategies were applied: 1) discarding all BQL observations (M1 method), or 2) implementing a different distribution for BQL (M3 method) with the LAPLACIAN option. Model selection was based on goodness-of-fit, feasibility and precision of parameter estimates, and likelihood ratio test or AIC comparison.

**Results:** Oxfendazole distribution was sufficiently described by a one-compartment model with first-order absorption and elimination. Oxfendazole exhibited less than dose proportional bioavailability. Oxfendazole apparent clearance ranged from 3.01 to 37.5 L/h and apparent volume of distribution increased from 40.9 to 508 L for a typical adult with ascending oral doses from 0.5 to 60 mg/kg. The model suggested that disposition of both metabolites was formation-rate limited, and oxfendazole sulfone pharmacokinetics were best characterized by one-compartment with the inclusion of both pre-systemic and systemic first-order metabolisms and first-order elimination.

**Conclusions:** The presented model was able to capture the pharmacokinetic profiles of oxfendazole and fenbendazole after single oral ascending doses of oxfendazole in healthy adults. This model will facilitate establishment of oxfendazole pharmacokinetics following multiple ascending dose and pharmacokinetics-pharmacodynamics correlation in recently completed or ongoing clinical trials (ClinicalTrials.gov Identifiers: NCT03035760, NCT03435718, NCT02636803) to support the translation of oxfendazole to human antiparasitic treatment.

**Table 3.** Pharmacokinetics of oxfendazole and metabolites following single ascending dose of oxfendazole from 0.5 to 60 mg/kg in healthy adults.

<table>
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<th>Parameter</th>
<th>Estimate (% CV)</th>
<th>IIV (ω²)</th>
<th>σ²</th>
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<tr>
<td>Oxfendazole (OXF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1*</td>
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<td></td>
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<tr>
<td>θ_1</td>
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<tr>
<td>θ_2</td>
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<td>V_{OXF}</td>
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<td>Oxfendazole sulfone (SULF)</td>
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<td>K_{SULF, gut}</td>
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Joint modeling of survival time and tumor size data in metastatic breast cancer

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Objectives: To explore the relationships between progression-free survival (PFS)/overall survival (OS) and longitudinal tumor size with joint modeling approach in metastatic breast cancer patients.

Methods: Data from 8 Phase III trials with 5 new drugs targeting metastatic breast cancer were involved in this study. Tumor size and PFS or OS data were analyzed simultaneously with NONMEM 7.3. And the joint model was evaluated by comparing the prediction of survival time and hazard ratio with the observed data.

Results: Bi-exponential tumor growth model was used to describe tumor growth dynamics in each arm. And predicted tumor size over time data was linked to the survival probability as a covariate in hazard function, which was best described using a lognormal survival model. Individual predictions of tumor size in joint model can well match the observed data. And the simulation results of survival time in each arm and hazard ratio in each trial suggested that the model could well describe the survival and tumor size dynamics over time except for the overall survival in patients with multiple previous treatments.

Conclusions: Joint models were built and evaluated to characterize the relationship between tumor growth and survival data in patients with metastatic breast cancer. These models may be useful to predict long-term outcome for patients based on the tumor size measurements.

The opinions presented are those of the authors and may not represent the position of the US FDA.

Population Pharmacokinetic and Exposure Efficacy Analyses of Deutetrabenazine in Patients with Moderate to Severe Tardive Dyskinesia

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Objective: Deutetrabenazine (Austedo, TEV-50717) is a highly selective vesicular monoamine 2 transporter (VMAT2) inhibitor approved in the US as a treatment for chorea associated with Huntington’s disease and tardive dyskinesia (TD). A population PK (popPK) model was developed to assess the individual systemic exposure to the active deuterated metabolites of deutetrabenazine, α-HTBZ and β-HTBZ in patients with moderate-to-severe TD and to evaluate the relationship between total(α+β)-HTBZ exposure and phase 3 efficacy parameters for these patients.

Methods: Rich PK data from phase 1 studies in healthy volunteers and patients with Tourette syndrome and sparse PK data from phase 3 studies of moderate-to-severe TD patients who received a total daily dose of 12-48mg deutetrabenazine were pooled to construct popPK models for each deutetrabenazine metabolite, α-HTBZ and β-HTBZ. Individual PK parameters of (α+β)-HTBZ were derived with the Posterior Bayes parameters and then merged with
efficacy data from the phase 3 study of moderate-to-severe TD patients. Three models (Emax with and without Hill coefficient γ, and linear) assessed the relationship between the primary endpoint, change in Abnormal Involuntary Movement Scale (AIMS) from baseline to week 12 and exposure parameters of total(α+β)-HTBZ (AUC, Cmin and Cave). Nonparametric analysis evaluated the relationship between proportion of subjects with 50% reduction in AIMS and Cave of total(α+β)-HTBZ. Logistic regressions evaluated the associations between the secondary endpoints, proportion of patients with improvement on Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC), and total(α+β)-HTBZ exposure.

Results: The popPK models of deutetrabenazine metabolite data suggested that each analyte was best described individually by a 2-compartment model, with a parallel mixed absorption/biotransformation processes (i.e. zero- and first order) and with a linear elimination process. Effects of CYP2D6 phenotype, body weight and age were covariates retained to explain variability of apparent clearance. The relationship between ΔAIMS and exposures of total(α+β)-HTBZ was best described by the linear model for ITT and mITT populations. Slopes of final models for both populations were similar and significantly different from 0 (p<0.05), indicating that higher exposure to total(α+β)-HTBZ would lead to greater decreases in AIMS score compared to baseline. Cumulative density function of ΔAIMS by Cave quartile showed that 31% and 47% of subjects with 50% reduction of AIMS were in the 3rd (36.3-64.0ng/mL) and 4th (36.3-64.0ng/mL) quartiles for Cave of total(α+β)-HTBZ (Fig 1 option). All logistic regression models detected a statistically significant (p<0.05) positive relationship between the probability of treatment success (i.e. “Much” or “Very Much” improved) on CGIC and PGIC and total(α+β)-HTBZ exposures (slope>0).

Conclusion: This study showed a positive exposure-response relationship between changes in the AIMS and improvement in the CGIC and PGIC ratings and total(α+β)-HTBZ exposure following daily dosing of deutetrabenazine for patients with TD.

Fig 1. Cumulative Distributions of Patients vs AIMS Change from Baseline (%) by Cave Quartiles

T-007

Exposure-response analysis to assess the concentration-QTc relationship of Psilocybin/Psilocin
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Objectives: Psilocybin, contained in some psychoactive mushrooms, is being investigated for its efficacy and safety in treating Major Depressive Disorder. Psilocybin is a prodrug readily dephosphorylated to psilocin that is metabolized in the liver by monoamine oxidases and mainly by glucuronidation. The objectives of the current analysis from a phase 1 clinical study are to evaluate the potential effects of psilocin exposure on QTc interval, and project the potential changes in QTc at the intended psilocybin therapeutic dose of 25 mg.

Methods: An open label single ascending dose study, at oral doses of 0.3, 0.45 and 0.6 mg/kg, was conducted in 12 healthy adults. Blood samples for PK assessment were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18- and 24-hours post-dose. 12-lead ECG were obtained at pre-dose, 2, 4- and 8-hours post-dose. A dose-proportionality analysis was performed to predict psilocin Cmax under the therapeutic dose of 25 mg. The relationship between psilocin concentration and the change from baseline in QTc interval (ΔQTc) was modeled using a population mixed-effects approach in Phoenix NLME®.

Results: The studied psilocybin doses ranged from 19 to 59 mg (0.3 to 0.6 mg/kg) and psilocin Cmax ranged from 11 to 54 ng/mL. No delay between psilocin PK and the change in QTcF was observed. The concentration-QTc analysis showed a positive effect of psilocin on QTcF prolongation with a linear relationship between psilocin Cmax and ΔQTcF. The upper bound of the 90%CI of the model-predicted mean ΔQTcF crosses the threshold of regulatory concern of 10 msec at a psilocin concentration of 31.1 ng/mL. However, this concentration is well below the expected range of psilocin Cmax under the psilocybin therapeutic dose of 25 mg. At a dose of 25 mg, the expected mean psilocin Cmax is 18.7 ng/mL and the associated upper bound of the 90% CI of the predicted mean ΔQTcF is 6.6 msec. In addition, in the psilocybin dose group of 26-31 mg, the closest dose group to the 25 mg therapeutic dose, the maximum observed psilocin Cmax was 30.6 ng/mL and the associated upper 90% CI of mean ΔQTcF is 9.9 msec. At doses about 2 times higher than 25 mg and at a psilocin Cmax about 3 times higher than the expected mean Cmax under 25 mg, ΔQTcF remains low with a mean predicted ΔQTcF of 9.1 msec and an upper 90% CI of mean ΔQTcF of 17.9 msec.

Conclusions: The concentration-QTc analysis suggests a mean QTcF prolongation of 6.6 msec at 25 mg psilocybin, with no expected psilocin accumulation under the intended clinical use of the drug.

T-008

A Pharmacokinetic Simulation Study to Assess Performance of a Sparse Blood Sampling Approach to Quantify Early Drug Exposure

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Objectives: The application of pharmacometric analyses to drugs used in emergency conditions is difficult as the setting can be chaotic and plasma concentrations problematic to obtain. Additionally, it may be early drug exposure that is more likely associated with the pharmacodynamic effect, so it is important to obtain an accurate estimate. An ancillary study of the Established Status Epilepticus Treatment Trial, which was a randomized, double-blind clinical trial comparing second line treatments of benzodiazepine-refractory status epilepticus, was designed to evaluate relationship between early drug exposure and seizure cessation. Early drug exposure for valproic acid (VPA) and levetiracetam (LEV) was estimated from two blood samples. The first sampling window was between 20-50 min (W1) and the other between 60-
The objective of this simulation study is to assess the performance and reproducibility of an early exposure metric using this 2-sample and NLME approach compared to the true simulation metric.

**Methods:**

**Step 1:** Literature-based population pharmacokinetic (PK) models for VPA (1-compartment) and LEV (2-compartment) were used to simulate concentration-time profiles without error (true) and with RUV error (R and mrgsolve) for 100 pediatric patients for each study drug after a fixed mg/kg IV dose. The true partial area-under-the-curve 0-2 hours (pAUC) was obtained by integrating simulated concentrations from 0 to 120 minutes (R and mrgsolve).

**Step 2:** From the noise-corrupted data, one timepoint in W1 and another in W2 were randomly selected for each patient.

**Step 3:** After fixing the population-level clearance and random effects terms to literature values, the 200 concentrations from the 100 simulated patients were analyzed under a population model (NONMEM) to provide individual EBE pAUCs 0-2 by integration.

To assess robustness and reproducibility of the methodology, a success statistic was defined as the percentage of subjects with a percent prediction error (PPE) within ± 20%. Steps 1-3 were repeated 100 times to obtain a distribution of the success statistic.

**Results:** The median (5th, 95th percentile) of the success statistic obtained using 100 simulated datasets was 89 (81, 93) for VPA and for LEV 92 (87, 96).

**Conclusions:** The PPE was within ± 20% in most cases and supports the 2-sample approach to quantify a metric of early drug exposure. Standard limitations exist, and these results are expected to be overly optimistic. It is assumed subjects in the study are similar to the literature population and exact times of dosing and sampling are known; concentrations are changing rapidly during early exposures and may be sensitive to model misspecification which was not incorporated into this analysis. Nonetheless, this encourages further investigation of pharmacometric models of drug response and factors affecting outcomes in difficult emergent settings.

**References:**

**T-009**

**Trial Simulation Framework to Inform a Comparative PK Trial of Pegaspargase in Pediatric Patients with Acute Lymphoblastic Leukemia**

**Authors:** Elliot Offman, Colin Chang, Samer Mouksassi, Sophie Peigne, Valerie Brunner, Alan Kugler

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3 Shire-Takeda, Lexington, MA, USA

**Background and Objectives:** Pegaspargase (Oncaspar®) is an approved PEGylated formulation of L-asparaginase, given to acute lymphoblastic leukemia (ALL) patients to ensure depletion of asparagine, ultimately resulting in leukemic cell death. Oncaspar is approved for administration via the intravenous (IV) and intramuscular (IM) route. As a complex, recombinantly-manufactured product, changes to the manufacturing process or formulation may result in altered pharmacokinetics (PK) for a newly developed form. The objective of this work was to inform the design of a potential comparative PK trial in support of a manufacturing change. A modeling and simulation approach was undertaken to estimate key elements such as sample size and sampling schedule needed to conclude the newly manufactured product is comparable to the marketed form.

**Methods:** Asparaginase activity (AA), which is a surrogate for L-asparaginase pharmacokinetics (PK), was determined following single dose IV and IM administration to pediatric patients with ALL, and fit to a population PK (PopPK) model in Phoenix NLME (Certara, v8.1). Trial Simulation (Certara, v2.3.0.3) was used to simulate the AA-time profile for 500 replicated trials (per route of administration) where the sample size varied and the proportion of subjects in each treatment arm were assumed to be equally split between the marketed and new forms. For each replicate, PK parameters were sampled from the variance-covariance matrix estimated from the PopPK model step. Exposure metrics (AUC, Cmax) were estimated for each treatment and compared by means of the two, one-sided t-test at an alpha error of 0.05, assuming a parallel group design. A trial was considered adequate where 80% of the simulated trials resulted in the 90%
confidence interval (CI) of the geometric least square means (GLSM) for AUC and Cmax parameters falling within 80-125%. Additionally, the proportion of subjects achieving AA above the clinically important threshold for AA of 0.1 IU/mL was estimated for each scenario.

**Results**: Pegaspargase following a single-dose IV administration was best described by a two-compartment model with saturable elimination from the central compartment and with body surface area (BSA) as a covariate on the central volume and Vmax parameters. IM absorption was characterized by a first-order process and 100% relative bioavailability to the IV formulation. Trial simulation suggested 80 and 120 subjects per treatment (parallel group) would be sufficient to achieve 80% power, assuming no difference in potency following the IV and IM, routes, respectively. In both scenarios, 100% of subjects would be anticipated to achieve and maintain AA above the clinically important threshold of 0.1 IU/mL.

**Conclusions**: Approximately 80 (IV) and 120 (IM) patients, per treatment (parallel group), are estimated to be required to achieve 80% power in a comparative PK trial in pediatric patients treated with pegaspargase for ALL.

T-010

**Population pharmacokinetic modeling of Opiranserin and its active metabolite in young and elderly adult subjects**

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**Institutions**: ¹Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea ²Vivozon, Inc. Seoul, Republic of Korea ³Department of Clinical Pharmacology and Therapeutics, Seoul National University Bundang Hospital, Seongnam, Gyeonggido, Republic of Korea

**Objectives**: Opiranserin (VVZ-149) is an investigational analgesic targeted for post-operative pain with a dual antagonistic action on GlyT2 and 5HT2A. This study was aimed to develop a population PK model for opiranserin and its active metabolite VVZ-368 in young and elderly adult subjects.

**Methods**: Two clinical study data were pooled to develop a population PK model. One was a single- and multiple-ascending dose study performed in 67 healthy adult subjects (aged 20 to 40 years; NCT01905410). The other was a single ascending dose study conducted in 12 middle aged and 12 elderly subjects (aged 50 to 64 and 65 to 84 years, respectively; NCT0233318). A loading-maintenance dose study data performed in middle aged subjects was used as a validation data set. Plasma concentration of opiranserin and VVZ-368 were analyzed from serial blood samples. Population PK model was developed using nonlinear mixed-effects method in NONMEM® software version 7.4 (ICON plc, Dublin, Ireland). Model parameters were estimated by first-order conditional estimation with interaction method. The inter-individual and the residual variability was modeled along with fixed effect parameters. The covariates (age, weight and creatinine clearance) were selected using stepwise forward selection and backward elimination method. The model qualification was performed using likelihood ratio test, graphical evaluation, visual predictive checks (VPCs) and bootstrapping.

**Results**: A total of 2,621 and 263 plasma concentration-time data were used to develop a population PK model and for model validation, respectively. The plasma concentrations of opiranserin and VVZ-368 were best described by a model with two parent compartments and a metabolic compartment. The model was parameterized in terms of the opiranserin clearance (CL), the central volume of distribution (V1), the peripheral volume of distribution (V2), the inter-compartmental clearance (Q), the opiranserin metabolic clearance converted into VVZ-368 (CLpm) and VVZ-368 clearance (CLv). The volume of the distribution of VVZ-368 (V3) was set equal to V1. Patient’s age showed a positive relationship with V1 and V2. The CL was 19.8% lower in the elderly subjects compared to young and middle aged adults. The typical values of CL, V1, V2, Q, CLpm and and CLv were 50.2 · (age/35) L/h, 16 · (age/35) L, 89.1 · (age/35) L, 98.6 L/h, 2.16 L/h and 0.802 L/h, respectively. The inter-individual variability (coefficient of variation, %) of CL, V1, V2, and CLpm were 20.5%, 35.2%, 20.6% and 47.4%, respectively. The proposed model was adequate, robust and showed good prediction performance based on goodness-of-fit plots, VPCs and bootstrapping results. The model also showed good prediction performance for validation dataset.
**Conclusions:** The final model adequately described the observed plasma concentrations of opiranserin and VVZ-368 in the young and the elderly subjects. The proposed population PK model can be applied for further drug development.

**T-011**

**Evaluation of the performance characteristics of azacitidine +/- pevonedistat (TAK-924) clinical trials using a mathematical model linking blast dynamics to hematologic improvement in patients with acute myeloid leukemia (AML)**

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**Objectives:** A semi-mechanistic, population PK/PD/efficacy model was developed using phase 1 data from patients with acute myeloid leukemia (AML) receiving pevonedistat (TAK-924) in combination with azacitidine. This model was used to conduct clinical trial simulations aimed at assessing the performance characteristics of clinical trials comparing efficacy of pevonedistat plus azacitidine versus single-agent azacitidine.

**Methods:** The model was built to predict how growth inhibition of leukemic tumor blasts would improve disease-related hematologic conditions over time, which enables estimating relevant clinical endpoints, such as composite complete remission (CCR), overall response rate (ORR) and progression-free survival (PFS). The dynamics of leukemic tumor growth were described using an evolutionary model, which assumed that drug-resistant leukemic blasts continuously grow irrespective of any therapeutic intervention, whereas drug-sensitive leukemic blasts grow before any drug treatment but get killed after pharmacological intervention with rates that depend on the drug(s) exposure. The dynamics of haematopoiesis were modeled using the Friberg model, which described the process of maturation of progenitor erythrocytes, neutrophil and platelet blasts into circulating hemoglobin, neutrophil and platelet cells. Three transit compartments were included to account for delay between synthesis of non-leukemic blasts and maturation of circulating cells. Feedback regulation was also included to account for modulation of blast synthesis mediated by circulating cells. Tumor growth was coupled to haematopoiesis by assuming that the leukemic blasts would inhibit the synthesis of non-leukemic blasts through an I\textsubscript{max} model.

**Results:** The model was calibrated using a non-linear mixed effects approach against data from the single-arm phase 1 study C15009 (NCT01814826) in AML patients receiving pevonedistat plus azacitidine. The final model was further qualified using visual predictive check corrected to account for dropout of non-responders. Using a Monte-Carlo approach, virtual clinical trials of pevonedistat plus azacitidine versus azacitidine were simulated to generate distributions of CCR, ORR and PFS and compute the probability of technical success (PTS) for each clinical endpoint. Predicted PTS for CCR, ORR and PFS were 93%, 98% and 86%, respectively. An extensive sensitivity analysis was performed to quantify the effect of the ratio between kill rates of sensitive leukemic blasts mediated by pevonedistat and azacitidine (k\textsubscript{SP}/k\textsubscript{SA}) on the predicted PTS. Modeling results indicated that the PTS for CCR and ORR remained above 80% if k\textsubscript{SP}/k\textsubscript{SA} was ≥0.73, whereas PTS for PFS was predicted above 80% only if k\textsubscript{SP}/k\textsubscript{SA} was ≥1.5, suggesting that the PTS for PFS is more sensitive to the relative kill strength of the two drugs compared to the other endpoints.

**Conclusions:** The proposed modeling framework provides a valuable tool to estimate performance characteristics that can be used to complement planned statistical analyses in powering clinical studies comparing the efficacy of azacitidine +/- pevonedistat in AML patients.

**T-012**

**Longitudinal Exposure-Response Analysis of Rectal Bleeding (RB) and Stool Frequency (SF) Scores in Patients with Moderate to Severe Ulcerative Colitis (UC) Treated with Tofacitinib**

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Objectives: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). This analysis characterizes the relationship between tofacitinib exposure and rectal bleeding (RB) and stool frequency (SF) scores over time in the studies OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951).  

Methods: Two Phase 3, randomized, double-blind, placebo-controlled 8-week studies were conducted using tofacitinib (10 mg twice daily [BID] and 15 mg BID) as induction therapy in patients with UC. RB and SF scores were evaluated at baseline and Weeks 2, 4, and 8 of the induction studies. The proportional odds model was applied to characterize the relationship between tofacitinib average plasma concentration (C_{avg}) and RB and SF scores in the induction studies. The longitudinal model was composed of baseline, placebo, and drug effect, where exponential time-course components were introduced into placebo and drug effect. A nonlinear mixed-effects modeling approach (NONMEM) was used for the analyses.

Results: The induction studies dataset included 680 males and 481 females, with a median age of 39 years. Dose-dependent reduction of RB and SF scores was observed over the 8-week treatment period. A proportional odds model with exponential time-dependent onsets of placebo and drug effects sufficiently described the time course of RB and SF response, with drug effect characterized by a linear C_{avg} relationship (parameter estimates are presented in Table). Model simulations suggest that patients receiving tofacitinib 10 mg BID achieved RB and SF score reduction by 1.06 and 1.01 at Week 8, respectively. The effect achieved at Week 2 was 67% and 62% of that at Week 8 for RB and SF, respectively.

Conclusions: The exposure-response model of the relationship between tofacitinib C_{avg} and RB/SF scores in patients with UC allowed quantitative characterization of efficacy onset, which is consistent with the observed efficacy onset based on partial Mayo score in patients with UC following initiation of tofacitinib induction therapy.  


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Rectal bleeding</th>
<th>Stool frequency</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>Estimate</td>
</tr>
<tr>
<td>B1</td>
<td>Logit value of Pr(Y≥1)</td>
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<tr>
<td>B2</td>
<td>Logit value of Pr(Y≥1)−Pr(Y≥2)</td>
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</tr>
<tr>
<td>B3</td>
<td>Logit value of Pr(Y≥2)−Pr(Y≥3)</td>
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</tr>
<tr>
<td>PMAX</td>
<td>Placebo maximum effect</td>
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<td>0.59</td>
</tr>
<tr>
<td>Phalf (week)</td>
<td>Half-life of placebo effect</td>
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<td>0.61</td>
</tr>
<tr>
<td>Dslope</td>
<td>Coefficient of C_{avg}</td>
<td>-0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Dhalf (week)</td>
<td>Half-life of drug effect</td>
<td>1.43</td>
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</tr>
<tr>
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<td>0.14</td>
</tr>
<tr>
<td>IIV_PMAX</td>
<td>IIV of PMAX</td>
<td>4.38</td>
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</tbody>
</table>

C_{avg}, average plasma concentration; IIV, inter-individual variability; Pr(Y≥n), cumulative probability of rectal bleeding or stool frequency score (Y)≥n; SE, standard error.

T-013

Use of a Semi-mechanistic Population Pharmacokinetic/Pharmacodynamic (Pop PK/PD) Analysis to study Exposure: Response (E:R) Relationships and drug efficacy in Acid Sphingomyelinase Deficiency (ASMD) Adult Patients Treated with Olipudase alpha, a Recombinant Human Acid Sphingomyelinase Enzyme.

Li Zhang¹, Jing Li¹, Catherine Ortemann-Renon², Judith Peterschmitt³, Alison Schecter³, Vanaja Kanamaluru¹⁰, Qiang Lu¹⁰
Objectives: ASMD is a rare, life-threatening lysosomal storage disorder that results from insufficient activity of the lysosomal hydrolase acid sphingomyelinase (ASM). Deficiency of ASM results in the accumulation of sphingomyelin (SM) and its key metabolites (lyso-sphingomyelin [lyso-SPM] and ceramide), leading to tissue damage and organ dysfunction including hepatosplenomegaly and pulmonary involvement. Olipudase alfa, is being developed as an intravenous (IV) enzyme replacement therapy (ERT) for the treatment of the nonneurological manifestations of ASMD. Olipudase alfa was shown to break down accumulated SM and lyso-SPM, reduce spleen volume and improve pulmonary function in adult patients. This analysis aimed to characterize the E:R relationship and to advance the understanding of the olipudase alfa treatment by developing a pop PK/PD model in adult ASMD patients.

Methods: Plasma lyso-SPM was selected as a pharmacodynamic (PD) biomarker for prediction of clinical efficacy of spleen volume reduction based on disease biology and after confirmation by statistical analysis of clinical data from 16 adult ASMD patients who received either a single dose (Phase 1a study), or multiple doses (Phase 1b study), a long term extension study of olipudase alpha IV treatment. A sequential approach was used by developing a Pop PK model, followed by the development of a Pop PK/PD model using model predicted olipudase alfa concentrations as exposure input to link the time course of PD biomarker (lyso-SPM) to that of the clinical endpoint (spleen volume). Demographic characteristics and baseline biomarkers (e.g. plasma lyso-SPM and ceramide) were tested as covariates by forward selection and backward elimination.

Results: A semi-mechanistic pop PK/PD model characterizing the relationship between olipudase alfa plasma concentration, lyso-SPM, and spleen volume was developed in ASMD adult patients. Olipudase alfa PK was described by a two compartment PK model with parallel linear and nonlinear Michaelis-Menten elimination. The time-course of plasma lyso-SPM reduction and subsequent spleen volume reduction were simultaneously described by indirect response models. Covariate analysis indicated: 1) olipudase clearance and volume of distribution increased with an increase in body weight, thus supporting the weight-based dosing regimen currently used for olipudase alfa clinical trials; and 2) a decrease in baseline spleen volume associated with lower baseline lyso-SPM in adult patients with ASMD.

Conclusions: A semi-mechanistic pop PK/PD model was developed which successfully integrates the highly relevant relationships between olipudase alfa exposure, PD biomarker (lyso-SPM), and a primary clinical endpoint (spleen volume) in adult patients with ASMD. By integrating major underlying pathophysiological mechanisms of ASMD, this model may facilitate predicting clinical response and guide dosing in individual ASMD patients.


T-014

A Review of Applications of Clinical Trial Simulation in the Past Decade

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Affiliations: Merck & Co., Inc., Kenilworth, NJ, USA

Objectives: To provide an updated review on the applications of clinical trial simulation (CTS), with a focus on applications on drug development and emerging trends since last reviewed in 2010.

Methods: Peer-reviewed journal articles matching the term “clinical trial simulation” published between Feb 1, 2010 and Mar 13, 2019 were retrieved from PubMed. Articles that presented or discussed the application of CTS were selected and reviewed. This work summarized information from these articles in terms of therapeutic area, objective of the work, source of data, type of model implemented, and design of the trial simulation. Methodological components, such as how uncertainty and variability were characterized, assumptions stated, and how virtual populations were handled, were also reviewed.
Results: A total of 76 papers were returned from the original PubMed search. Of those, 47 research papers and 14 reviews were included and summarized in the final review. Among the research papers, CTS was leveraged in multiple therapeutic areas, including oncology (n=10 articles), cardiovascular diseases (n=10 articles), neurology (n=9 articles), and infectious disease (n=5 articles). In terms of purpose, the most common applications for CTS in drug development included informing clinical study design (e.g., selection of dose and dosing regimens, sampling scheme, sample size) and predicting the probability of success for programs. These exercises allowed for more efficient late-stage studies. Noticeably, simulations for supporting post-marketing applications in academic and clinical settings seem to have emerged compared to the previous decade¹, including individualized treatments and alternative dosing regimens that differ from the label. Additionally, CTS was leveraged to evaluate clinical implications in special populations (e.g., pediatrics, obesity, n=7) and to assess several intrinsic and extrinsic factors, including: drug interactions (n=2), formulation change (n=2), pharmacogenomics (n=5), food effect (n=1) and QTc-interval prolongation (n=1).

Conclusions: This work demonstrates that CTS continues to be a critical component drug development, saving both time and cost by streamlining late-stage development. Additionally, there were many cases of exploration of alternative dosing strategies that may differ from the label and optimization of individualized treatment protocols for specific populations. There appears to be an emerging use of CTS in the post-marketing to optimize patient care, especially in academic and clinical settings. Looking forward, continued use of CTS is expected by broader audiences as it becomes more widely available and the value of modeling and simulation is recognized in patient care settings, as well as drug development.


Disclosures: ML and CD were employed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA at the time of this work.

T-015

Application of the Optimal Design Approach to improve Therapeutic Drug Monitoring of Busulfan in Children receiving Hematopietic stem cell transplantation (HSCT).

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Objectives: Busulfan is the most commonly used agent in Hematopoietic stem cell transplantation (HSCT) conditioning regimes, given alone or in combination. Considerable inter-patient variability exists in the effectiveness and toxicity of busulfan-containing conditioning regimens. Therefore, personalizing Busulfan doses improves the clinical outcomes, and it is clinically accepted due to a narrow therapeutic window. The objective of this study was to find a design that minimizes the uncertainty of population parameters used for busulfan dose prediction.

Methods: Data on 72 patients receiving Busulfan prior an HSCT (7 months-18 years, 5.1–47.0 Kg), suffering from immunodeficiencies or malignant diseases, was used to build a 2-compartment pharmacokinetic (PK) model of the drug. Busulfan (1-2 mg/Kg) was administered intravenously in a 2 or 3-hour infusion for four days prior HSCT, either every day, twice daily or every 6 hours. Blood samples to determine busulfan concentration in plasma were obtained prior the first administration, and 5, 10 and 30 minutes, 1, 2 and 4 hours after the end of the infusion. Once the PK model was built, a distribution of the population parameters was used in the optimization as prior information. The software PopED was used to perform optimal design of the sampling schedule. The covariates included in the PK model were taken into account in the optimization exercise (weight affecting the dose and the all the PK model parameters and age, affecting clearance).
**Results**: The optimized design considered the three different administration schedules of busulfan, so there is only one protocol of sampling extraction independently from busulfan administration schedule. The optimized sample times that rendered best performance than the protocol times were: 15 minutes after the administration of the drug, and 5 minutes, 35 minutes, 1 hour and 45 minutes after the end of the infusion, and the last sample right after the next administration. Therefore, the new design represents a 16.6% reduction (n=1) in sampling demanding with respect the current protocol. The efficiency of the optimized design with respect to the protocol was calculated to be 2.84, indicating significantly better performance of optimized design. The expected Residual Standard Errors (RSE%) of the parameters under the optimal designs were compared to the RSE% of the protocol, showing a reduction from 1 to 27% RSE in the parameters. In addition, prediction performance of the optimized design was evaluated, obtaining similar parameter precision compared to the protocol (maximum bias <10%).

**Conclusions**: An optimized sample times design for monitoring busulfan in pediatric patients under HSCT was developed. The evaluation of the reduced design suggests better performance than the original protocol, even reducing the samples per patient. We firmly believe that this work is of potential implementation in the clinical setting, improving patient care.

**T-016**

**A Model Based Meta-Analysis to study the effect of glucagon-like peptide (GLP-1) receptor agonists on body weight in obese and type 2 diabetic populations**

**Authors**: Akshita Chawla¹, Li Qin², Brian Maas¹, Nele Mueller-Plock², Eugène Cox², Sumit Basu¹, Matthew Rizk¹, John Maringwa², Larissa Wenning¹

**Institution**: (1) Merck & Co., Inc., Kenilworth, NJ, USA (2) Certara Strategic Consulting, Breda/The Netherlands and Basel/Switzerland

**Objectives**: This Model Based Meta-Analysis (MBMA) aimed to develop a comparator model that provides a quantitative framework for the comparison of treatment effects of GLP-1 agonists on body weight in type 2 diabetes and obesity patients, and as such support strategic and tactical decisions for the development of new drugs for weight loss. Average body weight change from baseline was considered as the primary endpoint for the analysis.

**Methods**: A systematic literature review was conducted to construct a GLP-1 database that consists of publicly available summary level safety and efficacy data from 147 trials (110 placebo-controlled) investigating 15 GLP-1 drugs. The primary source of information for this database is PubMed, clinicaltrials.gov, company registries, conference abstracts/posters/presentations, and regulatory reviews from FDA websites. A formal statistical meta-analysis of this database resulted in a model that captured the time course (onset) of dose response relationships of the GLP-1 agonists. The response in the MBMA model was described as the sum of a trial specific non-parametric (unstructured) placebo effect and a parametric drug effect depending on dose, time, model parameters and covariates. Dose response was estimated where possible, with drug-specific treatment effects using a shared Emax within a drug class and a drug-specific potency (ED50). The observations were weighted based on reported measures of precision. Covariates such as mean baseline body weight, indication, patient domicile status, and background therapy were graphically explored and tested for statistical significance. Model development, evaluation and simulations were performed in R 3.5.2. Model appropriateness was assessed using numerical and graphical diagnostics.

**Results**: A dose response relationship with an Emax model was identified for 12 of the 15 drugs and an overall drug effect was considered for the other 3 due to limited dose ranging. There was no evidence of differences in Emax and hence a shared Emax of approximately -10 kg was estimated for all GLP-1 drugs. Drug-specific onset of drug effect was not supported by the data and hence a shared onset of drug effect was estimated. Model diagnostics indicated that the model captured both dose response and time course trends in the data well. Baseline body weight and indication were strong drivers of treatment effect. This model allows us to simulate predicted treatment effect for marketed drugs. Results show that the mean body weight change difference from placebo for marketed drugs range from -7 to -1 kg (Figure) for type 2 diabetes while changes in obesity are expected to be somewhat larger.
Conclusions: In a MBMA framework for weight loss due to administration of GLP-1 drugs, model estimated treatment effects provided a quantitative framework for benchmarking new investigational compounds to existing drugs for weight loss in patients with obesity and type 2 diabetes.

Figure: Illustration of simulated treatment effect in type 2 diabetes at 24 weeks at the maximum dose for each drug for a baseline body weight of 91 kg. Points are the expected differences from placebo and lines span the 5th and 95th percentiles of differences based on 1000 sampled parameter estimates from the final model variance-covariance matrix.

T-017

Modeling Fibrosis Progression in NAFLD and NASH

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Objectives: The specific pathways, timescales, and dynamics driving the progression of fibrosis in NAFLD and NASH are not yet well understood. The objective of this work was to develop a continuous-time Markov Chain model [1] to capture the heterogeneity of fibrosis progression and regression observed in the clinic.

Methods: Published studies involving paired liver biopsies with varying trial duration were identified [2-8]. We then employed a continuous-time Markov Chain model (Fig. 1A) to estimate the average time of disease progression through the various stages of fibrosis. A sensitivity analysis was performed to identify which parameters have the most influence on the average change in fibrosis score.

Results: Model fitting suggests the average duration of progression from stage F0 to F1 is 2.44 months and 90% of patients transitioned from F0 to F1 between 0.13 and 7.3 months. This rate accounts for misclassification and is independent of time spent in a particular stage. Reverse rates were also estimated to account for disease regression. Sensitivity analysis revealed intervention at stage 1 and stage 2 results in improved overall average fibrosis scores for a typical patient cohort distribution (Fig. 1B). These results were in good agreement with a retrospective analysis of placebo controlled pioglitazone clinical trials for the treatment of NAFLD and NASH [9-11].
Conclusions: The continuous-time Markov Chain modeling approach enabled us to estimate forward and reverse parameters for fibrosis in NAFLD and NASH. Accounting for sample error variability and pathologist variability allows us to make more robust predictions about potential clinical outcomes. As more data becomes available, we will be able to increase confidence in parameter estimates which will allow us to make better predictions to aid clinical trial design.

Figure 1. A) Continuous-time Markov Chain model structure. B) Sensitivity analysis for p1 and p2.

References:

T-018

Impact of endogenous production on pharmacokinetics of one-compartment model having simultaneous first-order and Michaelis-Menten elimination

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2 Faculté de Pharmacie, Université de Montréal, Québec, Canada;
3 Centre de recherches mathématiques, Université de Montréal, Québec, Canada;

Objectives: Drugs have additional endogenous sources and exhibit simultaneous first order and Michaelis-Menten (M-M) elimination are becoming common in pharmacokinetic (PK) modeling. However, the numerical data fitting for parameter estimation is not sufficient for mechanistically explaining the fair impact of each model component. This study aims to delineate quantitatively these impacts on some main PK properties such as the area under the curve (AUC) that help for their rational estimations through establishing a closed form solution of concentration-time course (C(t)).
Methods: One-compartment PK model with simultaneous first order and M-M elimination and constant endogenous production rate \( (r_{prod}) \) for the case of a single intravenous bolus dose administration was studied. Advanced mathematical techniques were applied to present the analytical solutions of the model and PK parameters, mainly \( C(t) \) and AUC. The impacts of nonlinearity and endogenous production on AUC were investigated through numerical simulations.

Results: The closed form solution of concentration-time course \( C(t) \) of the model was established through a transcendent mathematical function [1]. Based on the corrected concentration as suggested in the FDA guidance [2], the explicit expressions of partial and total AUC were provided, and both were proved upper bounded by their parallels in the linear model, i.e., the studied model in the absence of the M-M elimination pathway. However, these AUCs always depend on \( r_{prod} \) although the baseline was subtracted from the observed concentrations. As a fact, larger values of \( r_{prod} \) lead to higher AUCs in a sigmoid way. Even after subtracting the instant contribution of concentrations from endogenous source, the net exposure of the administered drug remains dependent on \( r_{prod} \), which increases with \( r_{prod} \) to a final saturate level.

Conclusions: The closed form solution of concentration-time course of the studied PK model were successfully established. Moreover, we proved that, in the current model structure, the net exposure of the administered drug is always influenced by the endogenous source. This fact should be taken into account in the evaluation design of drug exposure.


T-019

Population Pharmacokinetic (POPPK) Analyses of Erthugliflozin (ERTU) in Select Ethnic Populations

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Affiliations: ¹Pfizer, Inc., Groton, CT, ²Pfizer, Inc., Beijing, China, ³Merck & Co., Inc., Kenilworth, NJ

*At the time of study conduct

Objectives: ERTU, a selective sodium glucose co-transporter 2 inhibitor, was recently approved for the treatment of adults with type 2 diabetes mellitus. Two POPPK analyses were conducted to characterize the ethnic sensitivity in ERTU pharmacokinetics (PK) for 1) East Asian (EA) versus Not East Asian (NEA) subjects and; 2) Asian subjects from mainland China versus Asian subjects from the rest of the world (ROW) and non-Asian subjects.

Methods: Data from up to seventeen Phase 1, Phase 2, and Phase 3 studies were included in the POPPK analyses. For the EA versus NEA analysis, race was categorized into two mutually exclusive groups: EA (N=154) or the reference NEA (N=2122). For the second analysis that included subjects from mainland China, race was categorized into three mutually exclusive groups: Asian subjects from mainland China (N=283), Asian subjects from ROW (N=427) and non-Asian subjects (N=2193). A two-compartment model with first-order absorption, lag time, and first-order elimination was fitted to the observed data. Interindividual variance (IVV) was included on apparent clearance (CL/F). Covariates were added to CL/F and apparent central volume of distribution (Vc/F) using the full model estimation approach. Bootstrap analysis was used to generate 95% confidence intervals (CI) for the final model parameters.

Results: For the EA versus NEA analysis, although the effect of EA on CL/F (95% CI) was significant based upon the CI from the bootstrap [1.17 (1.11-1.24)], individual post-hoc CL/F values were similar between EA [10.2 L/hr (5.94-18.2 L/hr)] and NEA groups [10.5 L/hr (5.28-19.2 L/hr)]. IVV on CL/F expressed as a coefficient of variation (CV) was 31.8%. Additionally, the effect of EA on Vc/F was also significant [2.48 (1.65-3.82)] relative to the NEA population. For the second analysis, mainland Chinese subjects exhibited a non-significant 4% increase in CL/F while Asian subjects from ROW exhibited a significant 8% increase in CL/F compared to non-Asian subjects when matched for all other covariates. IVV on CL/F expressed as a CV was 31.6%. Furthermore, mainland Chinese subjects and Asian subjects from ROW exhibited a significant 44% and 115% increase in Vc/F (mean [95% CI] of 1.44 [1.08,1.97] and 2.15 [1.53,2.99]), respectively, relative to the reference non-Asian subject.
**Conclusions:** Increases in Vc/F in both the analyses would result in a decrease in maximum concentration but would not impact area under the concentration-time curve (AUC). As glycemic efficacy of ertugliflozin is driven by AUC, these changes in Vc/F were not considered clinically relevant, nor likely to result in meaningful ethnic differences. Additionally, the differences in CL/F (AUC) were not clinically meaningful and are not expected to result in meaningful ethnic differences in the PK of ERTU.


**T-020**

**Model-based Dose Selection for a GnRH Receptor Antagonist in Endometriosis and Uterine Fibroids (UF) to Reduce Symptoms While Preventing Lumbar Spine Bone Mineral Density (BMD) Loss**

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¹ Metrum Research Group, Tariffville, CT, USA; ² R&D, ObsEva SA, Geneva, Switzerland.

**Objectives:** Linzagolix is a GnRH receptor antagonist in development for the treatment of endometriosis or UF symptoms. Analysis objectives were: (1) Develop longitudinal exposure-response models for dysmenorrhea (DYS, menstrual pain), non-menstrual and overall pelvic pain (NMPP, OPP), bleeding days, and BMD in endometriosis patients to support linzagolix dose selection in pivotal Phase 3 trials and (2) assess the viability of an estradiol (E2) target range as an efficacy and safety indicator.

**Methods:** Models for linzagolix pharmacokinetics (PK), E2, DYS, NMPP, OPP and BMD measurements were developed from 2 studies in patients with endometriosis and 3 healthy volunteer studies; 3 other patient studies served for model validation. Simulated daily linzagolix AUC derived from population PK drove changes in E2 over 24 weeks on treatment (dose range: 25 to 200 mg daily). Model-predicted E2 were used to drive changes in DYS, NMPP, OPP, and bleeding (efficacy), and BMD (safety). DYS, NMPP, OPP, and bleeding were modeled using logistic and zero-inflated beta regression models for repeated measures. BMD changes were described using a bone health quantitative systems pharmacology (QSP) model [1]. Candidate linzagolix doses were evaluated for likelihood of achieving pre-defined pain and BMD targets by integrated simulation from models for PK, PK-E2, E2-DYS, E2-NMPP, and E2-BMD. Candidate linzagolix doses for consideration in pivotal Phase 3 trials were those that lowered E2 sufficiently to meet pain (efficacy) targets while retaining enough E2 maintain BMD (safety) targets.

**Results:** Linzagolix PK was described by a two-compartment model with sequential zero/first-order absorption process (CL/F: 0.422 L/hr). E2 changes over time were well described as a function of linzagolix 24-hour AUC according to a sigmoid inhibitory Emax model (AUC⁰: 1.68 x10⁶ ng•hr/mL). Lower E2 values were statistically associated with decreased in DYS, OPP, and bleeding. The previously reported E2 target range (20 to 50 pg/mL) to balance efficacy and safety endpoints was confirmed. Scaling function parameter estimates in the BMD model were E2 fraction: 0.202, sigmoidicity parameter: 1.17 (Equation 6 in [1]). Linzagolix doses between 75 and 125 mg daily were expected to meet pain and BMD targets (98 to 100% probability). Doses of ≥ 100 mg daily resulted in relative reductions > 60% in bleeding from baseline. Of note, linking the endpoints directly to PK did not improve model performance, substantiating E2 as a safety and efficacy marker.

**Conclusions:** This modeling and simulation study indicated that linzagolix can target E2 ranges appropriately and determined suitable doses for consideration in pivotal Phase 3 endometriosis (75 to 125 mg daily) and uterine fibroid (100 to 125 mg daily) studies.

**References:** 1. Riggs MM, et al. (2012) CPT:PSP 1.: https://doi.org/10.1038/psp.2012.10

**T-021**

**Population Pharmacokinetic Modeling and Simulations of rhPTH(1-84), a Recombinant Human Parathyroid Hormone, to Determine Dosing in Pediatric Patients with Chronic Hypoparathyroidism**
**Authors:** Olivier Barriere, Nathalie H. Gosselin, Leng Hong Pheng, Jean-Francois Marier, Nicole Sherry, and Ivy Song

**Institutions:** Certara Strategic Consulting, Princeton, NJ, USA; Shire Human Genetic Therapies, Inc., Lexington, MA, USA, a member of the Takeda group of companies

**Objectives:** rhPTH(1-84), a full-length recombinant human parathyroid hormone (PTH), is approved as an adjunct to calcium and vitamin D to control hypocalcemia in adult patients with chronic hypoparathyroidism. Population pharmacokinetic (PK) modeling and simulations of rhPTH(1-84) following subcutaneous doses were performed to support dosing in pediatric patients with hypoparathyroidism.

**Methods:** Nonlinear mixed-effect modeling was used to assess the concentration-time profiles of PTH in adult patients with chronic hypoparathyroidism. A covariate analysis was performed to identify sources of variability using a stepwise approach. The area under the curve over 24 hours (AUC_{0-24}) in adult patients treated was used as the targeted exposure to optimize pediatric dosing. Simulations were performed in a virtual population of pediatric patients with chronic hypoparathyroidism treated with weight- or fixed-based once daily (QD) and twice daily (BID) regimens.

**Results:** A total of 135 adult patients with chronic hypoparathyroidism was included in the analysis. The PK of PTH was best described using a 1-compartment mixture model with a first-order absorption and first-order elimination. The apparent clearance (CL/F) and volume of distribution (Vc/F) were 86.1 L/hour and 2.78 L, respectively. Allometric functions accounting for the effect of weight on CL/F and Vc/F were included in the model (fixed exponents of 0.75 and 1, respectively). Baseline levels were included to account for low residual endogenous levels of PTH in a subset of patients. A mixture model was used to capture single or double absorption peaks. The population PK model resulted in an adequate prediction of individual concentrations of PTH. Virtual pediatric patients (0 to 17 years) with chronic hypoparathyroidism were simulated assuming no residual PTH gland function. The targeted range of exposure was 168 to 1465 pg.hour/mL, which corresponded to the 25th to 75th percentile of AUC_{0-24} values in adult patients treated with 25 and 100 µg rhPTH(1-84). The following dosing regimens in pediatric patients with chronic hypoparathyroidism are expected to result in exposure within the targeted range.

<table>
<thead>
<tr>
<th>Regimens</th>
<th>QD Dosing</th>
<th>BID Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight-Based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 kg:</td>
<td>0.72 µg/kg</td>
<td>≥10 kg: 0.36 µg/kg</td>
</tr>
<tr>
<td>&lt;10 kg:</td>
<td>1.07 µg/kg</td>
<td>&lt;10 kg: 0.54 µg/kg</td>
</tr>
<tr>
<td><strong>Fixed-Based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40 kg:</td>
<td>50 µg</td>
<td>≥40 kg: 25 µg</td>
</tr>
<tr>
<td>20 to &lt;40 kg:</td>
<td>25 µg</td>
<td>20 to &lt;40 kg: 12.5 µg</td>
</tr>
<tr>
<td>10 to &lt;20 kg:</td>
<td>12.5 µg</td>
<td>10 to &lt;20 kg: 6.25 µg</td>
</tr>
<tr>
<td>&lt;10 kg:</td>
<td>6.25 µg</td>
<td>&lt;10 kg: 3 µg</td>
</tr>
</tbody>
</table>

**Conclusion:** A population PK analysis was performed to support the development of an optimal dosing strategy for rhPTH(1-84) in pediatric patients with chronic hypoparathyroidism. Assuming a similar exposure-response relationship in adult and pediatric patients, the above dosing regimen in pediatric patients is expected to result in similar activity as in adults.

**T-022**

**Appropriate design of paediatric clinical trials - a careful balancing act?**

**Authors:** Navin Goyal, Khadeeja Mohammed, Daren Austin

**Institutions:** Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline

**Objectives:** Drug development in special populations such as pediatrics is very challenging. The current work describes approaches to address important design aspects of a paediatric clinical trial that makes full use of existing information. An efficient study design, capable of identifying determinants of exposure and response in children, is described.
Methods: Changes in paediatric legislation have brought considerable focus on the development of new medicines in children. Typically, this entails conducting a paediatric clinical trial to investigate pharmacokinetics (PK), pharmacology and efficacy. A wide age and weight range, challenges in recruitment and limited opportunities for pharmacokinetic sampling mean the design of such trials requires careful consideration.

A pediatric trial was designed optimizing the weight bands, doses, number of subjects and PK samples per subject to titrate to equivalent adult exposure. Some $10^6$ virtual paediatric patients were generated using a population pharmacokinetic model. From this virtual population, 1000 trials per scenario of sample sizes $2^6$ patients using either weight-band based stratification or no stratification were sampled. Four pharmacokinetic sampling schemes were considered for a drug with long terminal phase half-life: dense (12 samples: 6H - D84), medium (6 samples: D1-D84), low (4 samples: D3-D60), sparse (3 samples: D3-D29). For each of the $2^5x4x1000$ virtual trials, the data was fitted using a population pharmacokinetic model fixing selected parameters to adult values, as appropriate. For each subject, individual post-hoc Bayes estimated AUC(0-INF) was compared with known (i.e., simulated) value. Each trial was summarised by Root Mean Square Error (RMSE) and compared with target adult exposure. The RMSE measure of precision has greater clinical relevance than previously proposed coefficient of variation for clearance.

Results: Best overall trial performance was achieved with dense pharmacokinetic sampling (12 samples) in 64 subjects, with all parameters estimated from the trial data (Figure). Trial performance was, however, maintained by careful fixing of parameters. A low sampling (4 PK samples) design achieved similar RMSE precision by fixing macro constants: A/B, distribution rate ALPHA, absorption rate KA) to adult values.

Bodyweight stratification had no effect on trial performance due to adjustment in the model. The selected trial of 16 subjects, with four samples had median RMSE of 13.2 ug.hr.ml (90% percentile range 8.8 – 19.5), implying a precision of 14% compared with adult. The estimated CV% across weight bands ranged from 12-37%.

Conclusions: Paediatric trials typically have wider covariate range and smaller sample sizes than adult. These limitations necessitate simulation for appropriate trial design. Using this work, a paediatric trial of only 16 subjects with sparse PK sampling with regulatory acceptance is ongoing. The proposed approach leveraging adult data for simulation, with fixation of noninfluential parameters allows efficient exposure estimation in children using very sparse data.


T-023

Use of Population Pharmacokinetic Modeling and Simulation to Design a Bioequivalence Study of IV Baclofen

Authors: Natalie Schmitz¹, Prasad Tata², Robert Kriel¹, Adolfo Gomez³, John Schrogie³, Jim Cloyd¹, Lisa Coles¹

Affiliations: ¹College of Pharmacy - University of Minnesota, ²Sandoz Inc., ³Allaysis LLC.
Objectives: Baclofen, available in oral and intrathecal formulations, is a commonly used anti-spasticity medication. If abruptly discontinued, however, a withdrawal syndrome can ensue. An intravenous (IV) formulation of baclofen is being developed for use when oral administration is not feasible. Previous pharmacokinetic studies using 7.5, 11.5, and 15 mg IV infused over 10 and 60 minutes and 10, 15 and 20 mg oral doses (which assumed an oral bioavailability of 75%) resulted in similar dose-normalized total exposures as measured by area under the curve (AUC) but maximum concentration (C$_{max}$) comparisons exceeded standard bioequivalence criteria. To better assess acceptable combinations of IV dose and infusion times, a series of population pharmacokinetic (PPK) models and simulations was used to guide the design of a comparative clinical bioavailability study.

Methods: A PPK model was built using baclofen concentration-time data obtained from a clinical dose escalation study to simultaneously fit the IV and oral routes of administration. The effect of infusion duration on C$_{max}$ and AUC was evaluated by performing simulations using PPK estimates determined from this model. Ten simulations of 42 subjects (the proposed sample size for the comparative bioavailability study) were completed using a 20 mg oral dose and IV doses of 15 or 16 mg infused over 120, 180, or 240 minutes. The predicted concentration-time data were analyzed using non-compartment analysis (NCA). Assuming a 2-way crossover bioequivalence design of each simulated infusions and 20 mg oral baclofen dose, bioequivalence (virtual BE) was computed using 90% confidence (80-125% for C$_{max}$ and AUC) interval approach. Modeling, simulations, NCA, and bioequivalence testing were completed using Phoenix WinNonLin and NLME 8.0 (Certara, Mountain View, California).

Results: A two-compartment pharmacokinetic model, with first-order absorption, fixed lag time, and a covariate of weight on central clearance best fit the concentration-time data. Oral bioavailability was estimated to be 78.6%. Simulation results (figure 1) following 15 or 16 mg infused over 180 or 240 minutes consistently met bioequivalence criteria, suggesting that these dose regimens would have high likelihood of success, while simulations of 16 mg infused over 120 minutes resulted in C$_{max}$ values greater than predicted for oral dosing.

Conclusions: Based on the modeling and simulation of various infusions and results of virtual bioequivalence study, a single-dose, four-treatment, randomized, crossover, bioavailability study of baclofen comparing infusions of 15 mg over 180 minutes and 16 mg over 180 or 240 minutes with 20 mg of oral drug was designed. This work led to the successful and well powered comparative bioavailability study in healthy subjects.

Figure 1: Simulated IV baclofen average concentration-time profiles over 8 hours
The dashed, black line represents 20 mg oral baclofen, green line represents 16 mg infused over 120 minutes, blue line represents 15 mg infused over 180 minutes, orange line represents 16 mg infused over 180 minutes, and the red line represents 16 mg infused over 240 minutes.

T-024

Sleep Efficacy Exposure Response (ER) Analyses of data from two Phase 3 Trials of Oral Lemborexant, a Dual Orexin Receptor Antagonist, in Subjects with Insomnia Disorder

Authors: Bojan Lalovic1, Oneeb Majid2, Ishani Savant Landry1, Larisa Reyderman1, Margaret Moline1, Jim Ferry1, Ziad Hussein3

Affiliations: 1Eisai Inc., Woodcliff Lake, NJ, US; 2Eisai Limited, Hatfield, UK

Objectives: To evaluate lemborexant ER based on sleep efficacy endpoints: polysomnography, sleep diary, insomnia, fatigue severity scores and morning sleepiness, based on SUNRISE 1 [NCT02783729] and SUNRISE 2 [NCT02952820] Phase 3 safety and efficacy trials and inform lemborexant proposed therapeutic dosing.

Methods: SUNRISE 1 enrolled ~1000 insomnia patients, 86% female, 45% >65 years old and SUNRISE 2 enrolled approximately 900 patients, 68% female, 40% >65 years old. Treatments consisted of 5 or 10 mg daily lemborexant, placebo, and zolpidem in SUNRISE 1. ER assessments consisted of three sub-analyses:

A) Polysomnography (PSG) objective assessments from the month-long Phase 3 trial (SUNRISE 1) with latency to persistent sleep (LPS), sleep efficiency (SE), wake after sleep onset (WASO), WASO in the second half of the night (WASO2H) and total sleep time (TST).
B) Pooled subjective sleep diary endpoints from SUNRISE 1 and SUNRISE 2, sWASO, sSE, sTST, sleep onset latency (sSOL) and Insomnia and Fatigue Severity Index/Scores (ISI/FSS) over at least 6 months of treatment.
C) Morning sleepiness assessments from SUNRISE 2.

Lemborexant daily average exposures (Cav) were derived from a population PK model [Lalovic et al. PAGE abstract, 2019]. Linear mixed effects were used to model these repeated means in R. ER model parameters included fixed effect terms for lemborexant exposure, time, placebo treatment and concentration-by-time interactions, pre-specified demographic covariates (eg, age, sex, body weight, race) and between-subject variability terms. Linear mixed effects framework facilitated an evaluation of numerous models and endpoints under a full model covariate approach.

Results: The ER model-based analyses of PSG endpoints from SUNRISE 1 (Table 1) and pooled sleep diary endpoints from SUNRISE 1 and 2 indicated a consistent, clinically meaningful set of change from baseline estimates following 5 and 10 mg lemborexant. Change from baseline LPS, WASO, WASO2H and sSOL, sWASO significantly decreased; SE, TST, sSE and sTST significantly increased with Cav and time. Covariate effects in ER relationships were relatively small and not considered clinically important. Lemborexant exposure and time were associated with decreases of ISI/FSS and small relative covariate changes. No association between morning sleepiness and Cav was observed.

Conclusions: With the exception of morning sleepiness, which showed no ER relationship, the sleep efficacy measures under consideration indicated statistically significant and clinically meaningful effects of exposure and time. Covariate effects were relatively small and not considered clinically meaningful. These analyses support a 5 mg lemborexant as an effective starting dose.

Table 1. Model-Predicted Change from Baseline PSG Endpoints Following 5 and 10 mg Lemborexant – SUNRISE 1

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clinically meaningful change*</th>
<th>Dose</th>
<th>Median Change from Baseline (5th – 95th Percentiles)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 28</td>
<td></td>
</tr>
<tr>
<td>LPS (minutes)</td>
<td>Decrease of &gt; 15min</td>
<td>5 mg</td>
<td>↓16.9 min (15.0 – 18.6)  ↓20.5 min (18.9 – 21.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>↓17.7 min (15.8 – 19.4) ↓20.0 min (18.4 – 21.4)</td>
<td></td>
</tr>
<tr>
<td>SE (%)</td>
<td>Increase of &gt; 5%</td>
<td>5 mg</td>
<td>↑24.4% (23.8 – 25.2)  ↑22.9% (22.2 – 23.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>↑25.9% (25.2 – 26.5)  ↑23.4% (22.6 – 24.0)</td>
<td></td>
</tr>
<tr>
<td>TST (minutes)</td>
<td>Increase of &gt; 20min</td>
<td>5 mg</td>
<td>↑119 min (116 – 122)  ↑112 min (108 – 115)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>↑126 min (123 – 129)  ↑114 min (111 – 117)</td>
<td></td>
</tr>
<tr>
<td>WASO (minutes)</td>
<td>Decrease of &gt; 20min</td>
<td>5 mg</td>
<td>↓98.7 min (96.7 – 101) ↓87.5 min (85.0 – 89.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>↓104 min (102 – 105)  ↓91.4 min (89.1 – 93.6)</td>
<td></td>
</tr>
<tr>
<td>WASO2H (minutes)</td>
<td>Decrease of &gt; 10min</td>
<td>5 mg</td>
<td>↓54.6 min (53.0 – 56.1)↓47.8 min (45.8 – 49.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>↓57.6 min (56.1 – 59.1)↓50.7 min (48.9 – 52.5)</td>
<td></td>
</tr>
</tbody>
</table>

Based on Sateia, et al., (JCSM 2017), the following values for change from baseline were considered to be clinically meaningful changes in PSG parameters: LPS with a decrease of 15 minutes, SE with an increase of 5%, WASO with a decrease of 20 minutes. For WASO2H, there is no apparent consensus regarding a clinically meaningful change from baseline; for this analysis, it was stipulated that for each half of the night, a 10 minutes decrease in WASO2H would be considered clinically meaningful. ↓=decrease; ↑=increase; PI=5th and 95th prediction interval, based on fixed effects parameters (70 year old female)

T-025

Influence of the cytochrome P450 gene polymorphism (CYP2D6 and CYP2C19) on the pharmacokinetics of YL-0919 in Chinese healthy subjects: a population pharmacokinetic analysis

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1 Phase I Unit, Clinical Pharmacology Research Center, Peking Union Medical College Hospital and Chinese Academy of Medical Sciences, Beijing, China

Objectives: YL-0919 was a novel combined selective serotonin reuptake inhibitor (SSRI) and 5-HT1A receptor agonist inhibitor [1]. A phase 2 clinical study (NCT03404466) is now being conducted to explore the safety and efficacy in patients with MDD. Following oral administration, YL-0919 was quickly absorbed and exhibited a considerable interindividual variation on the mean elimination half-life (1.56~15.42 h). Genetic polymorphisms of metabolic enzymes might be the main cause based on in vitro studies. To evaluate the degree of the impact of different CYP2D6 genotypes and CYP2C19 genotypes on the PK variability of YL-0919 in a healthy Chinese population, a population PK approach was employed.
**Methods**: The pharmacokinetic profiles of YL-0919 were obtained in a first in human (FIH) study. A total of 69 healthy Chinese subjects were enrolled in this double-blind, random, placebo-controlled dose escalation study. CYP2D6*1, *2, *10, *41, *65 and 2C19 *1, *2, *17 polymorphisms were observed among these subjects. The base PK model was chosen by fitting two-compartment model to the concentration-time data, with zero-order oral absorption kinetic and first order elimination kinetics. The first-order conditional estimation (FOCE) method with the interaction option was used to estimate the PK parameters and their variabilities. The covariates included age, body weight, height, sex, BMI and different gene polymorphism classification methods.

**Results**: The allele frequencies of CYP2D6*1, *2, *10, *41 and *65 were 50.0, 16.7, 23.3, 3.3 and 6.7%, respectively. The allele frequencies of CYP2C19 *1, *2 and *17 were 78.3, 21.7 and 1.7%, respectively, which were close to those reported in the literature [2-3]. Classification method by activity scores of CYP2D6 reduced the OFV most by 12.9, compared to that of traditional classification method (dOFV: -7.5), and the individual variability of CL was reduced by 17.6%. Bootstrap analysis showed that the median parameter estimates were generally comparable with the estimates obtained using the NONMEM program, whereas the goodness of fit and the visual predictive check suggest that our PK model adequately described the original data.

**Conclusions**: Population pharmacokinetic analysis showed that the presence of reduce function allele of CYP2D6 may have effect on the main PK parameters of YL-0919. Further investigation was needed in a larger population and patients with depression to confirm whether dose adjustment will be required in clinical use.


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**T-026**

**Development of a mechanistic PK-PD model to guide siRNA therapies**

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**Objectives**: To develop a mechanistic model to identify the key processes that contribute to the efficacy of siRNA therapies and to build guidelines for selection of dosing regimen

**Methods**: A mechanistic PK-PD model with three physiological compartments, plasma, interstitial fluid, and target cells, was built. The processes that contribute to drug distribution, siRNA delivery to target cells, RNA interference on target mRNA and related protein were represented with an ODE model using MATLAB 2017b. The non-clinical and clinical PK-PD data related to RNA interference and siRNA therapies that were reported in literature was used to inform the model parameters. A local sensitivity analysis was performed to identify key mechanisms that contribute to exposure at the site of action, target engagement and efficacy.

**Results**: The mechanistic PK-PD model was used to identify the key processes that contribute to the efficacy of the siRNA therapy, and to predict the impact of these processes on the clinical outcomes for various dosing scenarios. First the relationship between target engagement and siRNA exposure in target cells was established. A local sensitivity analysis revealed that siRNA exposure is affected primarily by the stability of drug product in target tissue, the siRNA stability in target cells and drug uptake rate by target cells. Exploration of various dosing scenarios showed the importance of dosing frequency on the efficacy of the siRNA therapy in maintenance of target mRNA at desired level and thereby, the clinical outcomes such as reduction in target protein. The relationship between the optimum dosing frequency and the siRNA parameters, such as siRNA stability, EC50 and target mRNA turnover rate, was quantified using the model. Moreover, the model analysis provided insights about the processes that contribute to variability and uncertainty in clinical outcomes of siRNA therapies.
Conclusions: The findings in our study shed light on the key mechanisms impacting drug delivery and efficacy in siRNA therapies and provide guidance on the key principles for the selection of dose regimen in clinical studies for siRNA therapies.

T-027

Population Pharmacokinetic (POPPK)/Exposure-Response (ER) Analyses of Varenicline in Adolescent Smokers

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Affiliations: ¹Pfizer Inc., Groton, CT, ²Pfizer Inc., New York City, NY USA

Objectives: Varenicline is approved as an aid to smoking cessation in adults. Models were developed to characterize the POPPK of varenicline and to explore the relationships between varenicline systemic exposure and measures of efficacy [continuous abstinence rate (CAR) 9-12] and tolerability (nausea/vomiting incidence) in adolescent smokers.

Methods: The POPPK analysis included varenicline data from one Phase 4 and two Phase 1 studies while the ER analyses included clinical endpoints from the Phase 4 study. A 1-compartment POPPK model with first-order absorption and elimination fitted the observed data and was parameterized as follows: apparent clearance (CL/F), apparent volume of distribution (V/F), and first-order absorption rate constant (ka). ER data, including CAR 9-12, defined as the proportion of subjects with biochemically confirmed abstinence from week 9 to week 12, and nausea/vomiting incidence, were analyzed implementing a logistic regression model with the individual varenicline area under the concentration-time curve from zero to 24 hours (AUC24) values predicted from the final POPPK model. For both POPPK and ER analyses, covariates were introduced using the full model estimation procedure and bootstrapping generated 95% confidence intervals for the final model parameters.

Results: 1097 observations from 218 subjects and 238 observations from 238 subjects were included in the POPPK and ER analyses, respectively. CL/F increased with increasing body weight for the reference 70 kg, white, adolescent male subject in the POPPK analysis. The effect of female sex on CL/F was significant, but the magnitude of the effect was relatively small (18%). All other covariate effects on CL/F (black or other race) were not significant. V/F increased with increasing body weight but decreased by 24%, 15% and 14% for black race, other race and female sex, respectively. Decreases in V/F would result in an increase in maximum concentration but would not impact AUC24. As efficacy and safety of varenicline was driven by AUC24 in adult smokers¹, the changes in V/F were not considered clinically relevant. No significant relationship was observed for CAR 9-12 with increasing varenicline AUC24 in the ERP analysis of efficacy. A statistically significant trend was observed for the increase in nausea/vomiting incidence with increasing varenicline AUC24 in the ER analysis of tolerability. Additionally, the probability of nausea/vomiting incidence increased by 86% in females relative to males.
Figure 1. Varenicline Exposure-Response Relationships in Adolescent Smokers for Continuous Abstinence Rate Weeks 9-12 (A) and Nausea/Vomiting Incidence (B)

For Figure 1A, the dotted line represents the predicted probability of continuous abstinence at weeks 9-12. For Figure 1B, the dotted line represents the predicted probability of nausea/vomiting incidence. For Figures 1A and 1B, open circles show the observed probabilities in each of the six AUCss(0–24) bins. Exposure was set to zero for the placebo group. The box-and-whiskers plots at the bottom describe the distribution of the exposure data. The box itself indicates the difference between the first and third quartiles of the data, showing the spread of the data. The solid line in the middle of the box is the median value, and the whiskers indicate the range of the data or 1.5 × the interquartile distance, whichever is less. Open circles plotted outside the whiskers exceed these limits and may be considered outliers. Abbreviations: AUCss(0–24)=area under the concentration–time curve at steady-state for 24 hours, BID=Twice daily, CAR=Continuous Abstinence Rate, HBW=High Body Weight (>55 kg), LBW=Low Body Weight (≤55 kg), QD=Once daily
Conclusions: For adolescent smokers, varenicline pharmacokinetics were generally comparable with those of an adult population. The ER analyses for efficacy showed no significant relationships with AUC24. However, the ER analysis for tolerability showed that nausea/vomiting incidence increased with increasing AUC24, which is consistent with the results in adult smokers.


T-028

Development of a Translational Population Pharmacokinetic-Pharmacodynamic Model of mRNA-1944 Encoding Antibody Against Chikungunya Virus in Rats and Non-Human Primates

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¹Moderna Therapeutics, Inc, 200 Technology Square, Cambridge, MA 02139 ²Certara Strategic Consulting, Montreal, Canada

Objectives: mRNA-1944 is a novel intravenously (IV) administered investigational mRNA therapeutic, encapsulated within a lipid nanoparticle system, encoding antibody against chikungunya virus (CHIKV) infection. The objective of this analysis was to develop a semi-mechanistic population pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) model to understand interspecies translation, dose-response relationship, quantify unexplained inter-individual variability and guide dose selection for a first in human clinical study.

Methods: Plasma concentration time-profiles of mRNA-1944 (PK response), measured by bDNA, and CHIKV IgG (PD response), measured by ELISA, were available from rats (N=80) and non-human primates (N=22) receiving two weekly IV infusions of mRNA-1944 at doses ranging from 0.3 to 5 mg/kg. Plasma concentrations of mRNA-1944 were modeled using a 3-compartmental semi-mechanistic PK model. CHIKV IgG concentrations were modeled using a 2-compartment model where antibody production rate was modeled as a linear function of mRNA-1944 plasma concentrations. Body weight based allometric scaling approach was used to describe interspecies differences in PK and PD characteristics of mRNA-1944 and CHIKV IgG, where volume exponents were fixed to 1 and clearance exponents were estimated. The model was subsequently used to predict a relationship between mRNA-1944 dose and CHIKV24 IgG response in humans.

Results: PK and PK-PD models adequately described the time-course of mRNA-1944 and circulating CHIKV IgG concentrations in rats and non-human primates with no evidence of systematic bias. Body weight based allometric scaling adequately described mRNA-1944 PK in rats and non-human primates with an estimated exponent of 0.65 for clearance parameters. CHIKV IgG levels seen in circulation increased linearly with an increase in plasma mRNA-1944 concentrations in both rats and non-human primates with a slope estimate (%RSE) of 4.6 (11.5). Clearance parameters of the CHIKV IgG PD scaled allometrically with body weight between rats and non-human primates with an estimated exponent of 0.78. Mode estimated median (%CV) terminal t½ of mRNA-1944 in rats and non-human primates was 5.2 (25.4%) and 11.6 (22.1%) hours, respectively. Mode estimated median (%CV) t½ of CHIKV IgG in rats and non-human primates was 15.5 (41.8%) and 26.2 (39.0%) days, respectively. Based on model simulations, selected first in human doses were 0.1, 0.3, 0.6 and 1 mg/kg, administered as a 1-hour IV infusion.

Conclusion: The semi-mechanistic PK-PD model adequately described PK and PD of mRNA-1944 in rats and non-human primates. Translatability of PK and PD between rats and non-human primates provides rationale for predicting dose-response in humans. Model predictions will be confirmed with data emerging from an ongoing Phase 1 clinical study in healthy adults testing single IV infusions of mRNA-1944.
Age-structured Population Model of DNA-label Distribution During Cell Cycle

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Objectives: DNA-binding fluorescent labels are applied to quantify the number of cultured cells in G₀/G₁, S, and G₂/M phases cell cycle using flow cytometry. Distributions of the DNA-fluorescence used to determine only a fraction of cells in each phase. In result, the dynamics of DNA distribution is not utilized for analysis of cell cycle data. The objective of this study is to use a mathematical model of DNA distributions in the phases of cell cycle to describe their time evolution in growing cell culture.

Methods: The PANC-1 cells were cultured in over four days. Each day the cells were harvested to obtain total cell counts. For cell cycle analysis, cells were fixed and stained with propidium iodide (PI). The PI fluorescence distribution was acquired by a flow cytometer. The fluorescent signal readings were converted to the density histograms in MATLAB. The final data consisted of a series of PI-histograms and the cell counts for four days. The McKendrick-Von Foerster model was adopted to describe the cell age distribution in the three cell cycle populations (see Fig. 1). The transitions of cells between the phases were described by constant hazards ($\mu_{G1}, \mu_S, \mu_{G2}$). The age-structured model implemented mechanisms for restricted cell growth ($N_{SS}$), and cell contact inhibition ($I_{max}, I_{50}$, and $\gamma$) introduced. The model parameters also included the initial cell counts in each phase ($N_{G10}, N_{S0}, N_{G20}$). The PI density distributions and cell count data were jointly fitted by the age-structured model using the maximum likelihood estimator implemented in fminsearch MATLAB function.

Results: Both PI histograms and cell count time courses were well captured by the age-structured population model. Parameter estimates were $\mu_{G1} = 0.18 \text{ 1/h}$, $\mu_S = 0.12 \text{ 1/h}$, $\mu_{G2} = 0.15 \text{ 1/h}$, $N_{G10} = 102,000 \text{ cells/mL}$, $N_{S0} = 94,000 \text{ cells/mL}$, $N_{G20} = 50,000 \text{ cells/mL}$, $I_{max} = 0.99$, $I_{50} = 20 \text{ h}$, $\gamma = 1.0$, $N_{SS} = 1480000 \text{ cells/mL}$. The model predicted duration of a cell cycle for PANC-1 cells was 21 h. The age distribution in S phase evolved from the initial uniform distribution to one with the median DNA increasing over time. The predicted DNA synthesis rate in S phase was initially equal to $\mu_{G1} N_{G10}/N_{S0} = 0.2 \text{ 1/h}$ and increased with time. The cell counts in all phases also increased in time.
Conclusions: The dynamics of flow cytometry DNA-label distributions in cultured cells can be adequately described by the age-structured population model. In addition to the cell number in three cell cycle phases, the model can predict the time course of DNA synthesis rate in the S phase. The age structure allows for extension of the model to account for drug effects both on hazards of transition between the phases and intracellular processes controlling the cell cycle.

T-030

Quantitative Analysis on the Relationship between Demographic Characters and Efficacy on the Longitudinal Change of Hot Flashes: A Model-based Meta-analysis (MBMA) in Patients with Vasomotor Symptoms (VMS)

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Objectives: Several researches on the association between patient characteristics and hot flashes have been reported. However, investigation of covariates on the efficacy of treatments using MBMA has not been performed. The objective of this analysis is to identify significant covariates which affect the time course of the treatment efficacy.

Methods: A systematic literature search was conducted in Scopus, Embase, and PubMed. Five drug classes were encompassed by this analysis, including (1) estrogens, (2) conjugated estrogens/selective estrogen receptor modulators, (3) selective serotonin reuptake inhibitors: paroxetine, (4) gabapentinoids: gabapentin and (5) neurokinin 3 receptor antagonists. Double-blinded, randomized, controlled studies were extracted. Moreover, based on the draft FDA guidance for clinical evaluation [1], studies of which inclusion criteria was more than seven moderates to severe hot flashes per day at baseline were used to build a dataset. An empirical structural model was constructed to describe the time course of hot flashes. The model was developed using NONMEM (Ver.7.3.0).

Results: A total of 11,543 subjects in 102 arms of 33 studies were obtained from published 32 literatures. An exponential model was used to describe the time course by an increasing form of the exponential decay function: $1 - \exp(-k \times \text{time})$, where $k$ determines the onset. The model was reasonably fitted to the data and used as a base model. After graphical examination of relationship between study or between-arm variability and potential covariates, age, body mass index (BMI) and time since last menstrual period were considered relevant to proceed to further testing. The covariates were incorporated one by one, and statistically significant decrease of the OFV (< 0.01) was observed in the relationship between BMI and the placebo effect and between time since last menstrual period and the placebo effect. The effect of BMI on the placebo effect was included in the first step. In the second step, no statistically significant decrease was observed in any of other covariates, and no more covariates were included.

Conclusions: This analysis showed that the factor which is reported to be associated with VMS can be also detected using the data at aggregate level. The effect of BMI was not selected in the similar analysis using placebo model [2]. The difference of results can be due to the integration of active arms or the selection criteria in the literature search.


T-031

Towards Achieving Regulatory Endorsement of a Disease Progression Model-based Clinical Trial Simulation Tool for Duchenne Muscular Dystrophy – An Exemplar using Clinical Data from the North Star Ambulatory Assessment
Karthik Lingineni¹, Daniela J Conrado², Diane Corey², Micki Hill³, Jane Larkindale², Klaus Romero², Stephan Schmidt¹, Sarah Kim¹, *, on behalf of the Cooperative International Neuromuscular Research Group (CINRG) investigators and Duchenne Muscular Dystrophy Regulatory Science Consortium (D-RSC) members

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**Objectives**: As drug development for Duchenne Muscular Dystrophy (DMD), a fatal genetic X-linked pediatric disease, has accelerated over the past decade, the consequent growth in the number of clinical trials is an opportunity and lack of drug development tools is a challenge in designing the trials. The objective of this research was to inform clinical trial design of studies to investigate efficacy of potential therapies for DMD through quantitative disease progression modeling and simulations using the North Star Ambulatory Assessment (NSAA) as an endpoint.

**Methods**: This disease progression model was developed based on extensive longitudinal individual patient-level data from four natural history studies and past clinical trial control arms. NSAA is a 17-item rating scale measuring functional motor abilities in ambulant children with DMD, and this scale ranges from 0 to 34 which is the maximum score indicating fully independent function. NSAA scores were excluded from this study if there was no age information or it was assessed at age lower than 4 years. The final analysis data set included a total of 476 individuals with DMD from 4 to 20 years of age with a total of 2,550 scores. To quantitatively describe the progression of DMD over time, several mathematical functions, including quadratic, Bateman, E\text{max}, sigmoid E\text{max}, and indirect response, were tested. Steroid use was tested as a categorical covariate i.e. with or without steroids. The model was developed in R-software (version 3.4.3) using nlmixr library (version 1.0.0-8).

**Results**: The sigmoid E\text{max} model best captured the time course of NSAA scores. A logit transformation was used to constrain the maximum fractional decrease in NSAA score (\(DP_{\text{max}}\)) between 0 and 1. The estimated \(DP_{\text{max}}\) was 86%. The estimated age at which NSAA score is half of its maximum decrease (\(DP_{50}\)) was 10 years, which is in line with that of reported in literature, as previous reports have shown that patients from age 7-14 typically go through a period of rapid decline in lower extremity motor function leading to loss of ambulation. The estimated Hill coefficient was 9.64. Steroid use was found to be a significant covariate on \(DP_{50}\), and the estimated mean value of \(DP_{50}\) increased by 14% when a steroid was used, which indicates a slower rate of disease progression.

**Conclusions**: The developed sigmoid E\text{max} model can be further improved by incorporating other potential covariates. This disease progression model provides an exemplar for developing further comprehensive univariate or multivariate DMD progression models using other endpoints together. The model-based clinical trial simulation tool will inform clinical trial design by informing inclusion/exclusion criteria, enrichment strategies, stratification approaches, timing and selection of clinical assessments, and trial duration and sample size for studies evaluating therapeutic candidates for DMD.

T-032

Population pharmacokinetic analysis of dupilumab in adult patients with chronic rhinosinusitis with nasal polyposis

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**Objectives**: Dupilumab, a fully human anti-interleukin (IL)-4Ra monoclonal antibody, inhibits signaling of IL-4/IL-13, key drivers of type-2 inflammatory disease. Dupilumab is approved for treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis (AD) and with moderate-to-severe asthma. Dupilumab also demonstrated positive efficacy for the treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) patients.
This analysis aimed to develop a population pharmacokinetic (PopPK) model for dupilumab and assess the influence of intrinsic and extrinsic factors on dupilumab PK in CRSwNP patients.

**Methods:** The analysis was conducted using pooled PK data at the dose of dupilumab 300 mg every week (qw), every two weeks (q2w) and every four weeks (q4w) from one phase 2 study and two pivotal phase 3 studies in adult CRSwNP patients. Taking into account the similarity in the observed dupilumab PK profiles across populations, the model structure from previous PopPK meta-analysis of dupilumab in adult healthy subjects, AD and asthma patients [1] was utilized to fit the sparse data from CRSwNP patients with only estimating key PK parameters (e.g., central volume distribution and elimination rate). Demographics, baseline lab parameters of liver and renal function, baseline biomarkers/disease severity, and anti-drug antibody (ADA) were evaluated in covariate analysis. The final model was validated with visual predictive check and bootstrap.

**Results:** The PopPK dataset included 465 CRSwNP patients with 1974 dupilumab concentrations. The dupilumab PK in CRSwNP patients were adequately described by a 2-compartment model with parallel linear and nonlinear Michaelis-Menten elimination plus first-order absorption. Weight was the primary source of variability in PK. Compared with a typical 79 kg (median) patient, steady-state area under concentration time curve was 35.1% lower in a 110 kg (95th percentile) patient and 56.8% higher in a 53 kg (5th percentile) patient, at the dose of 300 mg q2w. All other covariates, including age, gender, race, laboratory parameters, biomarkers/disease severity, and ADA were not found to have statistically significant effect on dupilumab PK in CRSwNP patients. Moreover, concomitant medications and comorbidity with asthma had no effect on dupilumab PK.

**Conclusions:** The PopPK model adequately described dupilumab PK in CRSwNP patients and enabled robust prediction of individual exposure. The PK properties and PopPK model of dupilumab in CRSwNP patients are comparable to those of AD and asthma patients. Only body weight exerted a noticeable effect explaining between-subject variability in dupilumab PK in CRSwNP patients, but, given the magnitude of the effect on exposure and the limited difference in efficacy/safety, dose adjustment for weight is not warranted.


T-033

**A Population Pharmacokinetics and Pharmacodynamics Model of L-Ornithine Phenylacetate in Patients with Hepatic Cirrhosis**

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**Objectives:** L-ornithine phenylacetate (LOPA) is an ammonia scavenger under development by Mallinckrodt for the management of hyperammonemia associated with hepatic encephalopathy (HE). In plasma, LOPA dissociates into two active moieties, ornithine (ORN) and phenylacetate (PAA). PAA works by covalently attaching to glutamine, which is formed when glutamate combines with ammonia. The product phenylacetylglutamine (PAGN), an inactive metabolite, is then eliminated through the urine. ORN is taken up by muscle tissue and converted into glutamate, thereby increasing the pool of glutamate available to combine with ammonia. The aim of this analysis is to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of LOPA in cirrhotic patients.

**Methods:** A semi-mechanistic population PK/PD model (Figure 1) was developed, for ORN, PAA, PAGN and ammonia, using 5565 plasma concentration data from two clinical studies, HE201 and HE209. In HE201, 1g, 3g, 10g, 20g and 40g over 4-hour intravenous (IV) infusion, or 10g, 20g, and 40g over 24-hour IV infusion were administered in stable cirrhotic patients. In HE209, 10g, 15g and 20g over 24-hour IV infusion were administered in hospitalized cirrhotic patients with HE. Standard of care therapies such as lactulose and rifaximin were allowed. Plasma samples were analyzed for ORN, PAA, PAGN and ammonia concentrations. Population PK/PD model was developed with NONMEM v7.4.
**Results:** ORN, PAA and PAGN concentration profiles were best described by one-compartment models. ORN exhibits linear PK at tested dose range. At doses above 10g of LOPA, conversion of PAA to PAGN starts to become saturated. Therefore, Michaelis-Menten equation was used to describe PAA’s conversion to PAGN. This elimination term thus represents PAGN formation. $\text{CL}_{\text{PAGN}}$ is the clearance of PAGN via urine. Plasma ammonia level was modeled with an indirect response model including the endogenous turn over as well as the removal of ammonia from both LOPA and other routes such as standard of care. Covariate effects of Child-Pugh score and body weight were identified to impact ORN and PAA clearance and volume of distribution. Creatinine clearance was identified as a covariate for PAGN clearance.

**Conclusions:** The model adequately described the PK/PD of LOPA in cirrhotic patients. Body weight, hepatic and renal functions are significant covariates. This PK/PD model is being used for dose selection for pivotal study.

**References:**

Figure 1. Population PK/PD model for L-ornithine phenylacetate

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**Population Pharmacokinetic Modeling and Exposure-Response Analysis of Probuphine® implants in Opioid Use Disorder Subjects**

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**Institutions:** ¹Certara Strategic Consulting, Princeton, NJ, USA; ²Markus Jerling Consulting AB, Stavgradsgatan, Bromma, Sweden; ³Titan Pharmaceutical, Inc., South San Francisco, CA, USA.
Objectives: Probuphine® (buprenorphine) implant, a six-month maintenance treatment for opioid-use disorder (OUD) in eligible patients is approved by the US FDA and Health Canada. A population pharmacokinetic (PK) model of buprenorphine (BPN) was developed to describe its release following administration of sublingual (SL) BPN or Probuphine implants in OUD subjects. Exposure-response analysis was conducted from Probuphine Phase 3 studies to assess the relationship between BPN and percentage of opioid-negative urines with self-reported use.

Methods: Nonlinear mixed-effect modeling was used to assess the concentration-time profiles of BPN in opioid-dependent adults. Covariate analysis was conducted based on stepwise forward addition and backward elimination procedure. To perform the exposure-response analysis, average BPN ($C_{avg}'$) were derived from individual BPN concentrations observed at Weeks 1, 4, 8, 12, 16, 20 and 24 following Probuphine implantation in Phase 3 studies and were merged with percentages of opioid-negative urines with self-reported use from Weeks 1-24. Categories of responders were defined as the proportion (>50% or >30%) of opioid-negative urines from Weeks 1-24.

Results: A total of 363 OUD subjects treated with SL BPN doses and/or Probuphine implants were included in the population PK analysis. BPN released from Probuphine implant was best characterized by a model including two depot compartments with fractions of implant dose being released from quick- and slow-depots. The first-order rates of BPN release from implant depot compartments were independent from that of the SL BPN depot. A peripheral compartment for systemic BPN was required to fit the slow elimination phase after SL administration. Only body weight on apparent clearance and body mass index on first-order rate of slow absorption were statistically significant.

The relationship between plasma BPN $C_{avg}'$ and percentage of opioid negative urines was modeled using linear and Emax models. A simple Emax model without intercept was found to provide the best fit of the data. The model indicates that 77.9% of theoretical maximum possible effect is achieved at plasma BPN $C_{avg}'$ of 0.638 ng/mL from the slow-release phase for 4 implants. Higher values of plasma BPN do not enhance efficacy significantly in this model. No noticeable impact of demographic characteristics was observed between $C_{avg}'$ of plasma BPN and opioid-negative urines.

A linear increase in logit of the probability for both responses (i.e., >30% and >50%) with BPN $C_{avg}'$ was estimated by logistic regression (p<0.05). For both endpoints, similar proportions of responders were observed on quartiles 2, 3, and 4 (31.1% vs 34.6% vs 32.7 % based on percentage greater than 50%; and 44.7% vs 44.2% vs 45.2% based on percentage greater than 30%), indicating a plateau in the plasma BPN effect around 0.56 – 0.85 ng/mL.

Figure: PK/PD Relationship between $C_{avg}'$ of Plasma BPN and Percentage of Opioid-Negative Urines
T-035

Exposure-response analysis for efficacy and safety of IDH305, a novel IDH1 inhibitor, in advanced cancer patients

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Objectives: A first-in-human phase 1 clinical trial evaluated IDH305, a potent allosteric isocitrate dehydrogenase 1 (IDH1) inhibitor, in patients with advanced malignancies harboring IDH1*R132 mutations following oral administration. Exposure-response (ER) relationships for efficacy and safety were characterized to assess the therapeutic margin of IDH305.

Methods: As of the data cut-off Nov 30, 2016, 166 patients were treated with IDH305 at dose levels from 75 to 900 mg twice daily (BID). Early antitumor activity was observed in acute myeloid leukemia (AML) patients. Reversible hepatotoxicity was also observed. Observed PK, efficacy and safety data were utilized in the ER analysis. PK measures evaluated include the geometric mean of IDH305 trough concentration (C\text{trough}) up to the event or the censoring and steady state AUC\text{0–12h}, both derived from non-compartmental analysis. Efficacy data are the best overall response of complete response (CR)/CR with incomplete blood count recovery (CRi) / partial remission (PR) before any new anti-cancer drug was taken. Hepatotoxicity data includes newly occurred or worsened grade 3+ (G3+) alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and bilirubin elevation. Exposure-response analyses evaluated the exposure-efficacy relationship in AML patients and the exposure-hepatotoxicity relationship in all patients regardless of cancer type. The relationships between the probability of observing a hepatotoxicity event or an efficacy event and IDH305 C\text{trough} were characterized by logistic regression models. The relationship between the first occurrence of hepatotoxicity and the duration of treatment was also explored. Assessment of the relationship between time to the first hepatic toxicity event and IDH305 C\text{trough} using cumulative incidence plot and Cox regression model was conducted. The effects of intrinsic and extrinsic factors were evaluated.

Results: C\text{trough} is selected as the PK measure in the ER analysis for efficacy and hepatotoxicity based on model selection criteria (AIC, SC, -2logL) and representativeness of PK exposure during treatment. The exposure-efficacy analysis in AML patients demonstrated that the probability of response (best overall response is either CR, CRi or PR) is positively associated with IDH305 C\text{trough}. Exposure-safety analysis demonstrated that IDH305 C\text{trough} may be associated with G3+ bilirubin elevation, but not with G3+ ALT/AST elevation. No significant covariate was identified in the relationship of probability of G3+ bilirubin vs. exposure or efficacy response vs. exposure. Age and prior antineoplastic radiotherapy were identified covariates in the relationship of G3+ ALT/AST vs. exposure; however, their influence may be due to imbalanced distributions across different disease indications.

Conclusions: Exposure-response analysis of efficacy and safety allowed a quantitative characterization of IDH305 benefit and risk profiles. The analysis informed clinical decision in early oncology development for IDH305.

T-036

Extending dosing interval of bintrafusp alfa (M7824) from every 2 weeks to every 3 weeks dosing

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²Merck KGaA, Darmstadt, Germany
³Occams Coöperatie U.A., Amstelveen, The Netherlands
**Objectives:** Bintrafusp alfa* (M7824), an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β “trap”) fused to a human IgG1 mAb blocking PD-L1, showed a manageable safety profile and encouraging efficacy in patients with heavily pretreated advanced solid tumors in phase 1 studies. The recommended phase 2 dose (RP2D) for monotherapy studies is 1200 mg every 2 weeks (Q2W). Here, we describe selection of bintrafusp alfa every 3 weeks (Q3W) as RP2D for combination studies with chemotherapies, which follow Q3W dosing cycle using simulations based on a previously described population pharmacokinetic (PPK) model [1].

**Methods:** PPK-based simulations were used to derive exposures meeting the criteria for selection of Q3W RP2D. Exposure criteria were: 1) trough and time-averaged concentrations at steady-state (C_{trough,ss} and C_{avg,ss}) should be similar or higher to those achieved with 1200 mg Q2W dosing; 2) most subjects should achieve the target C_{trough,ss} of 50 µg/mL defined based on PK-PD correlation analyses [2]. Simulations based on the available PPK model [1] were used to select the Q3W dose that meets above exposure criteria.

**Results:** With 2400 mg Q3W dosing, the projected geometric mean C_{trough,ss} and C_{avg,ss} were 88% and 133%, respectively of those at 1200 mg Q2W; 88% of the subjects are predicted to achieve the target C_{trough,ss}. The available safety and exposure data from phase 1 studies support further safety and efficacy evaluation of 2400 mg Q3W dose. The highest dose level with completed dose limiting toxicity evaluation in phase 1 studies was 30 mg/kg Q2W and maximum tolerated dose was not reached; evaluation of a 2400 mg Q2W cohort is ongoing. For a typical subject receiving 2400 mg Q3W dose, the exposure margins for AUC and end-of-infusion concentration (Ceoi) are projected to be ≥1, relative to the exposures achieved in phase 1 studies. Adverse events incidences were generally weakly or not correlated with exposures, including no correlation between the probability of infusion-related reactions and Ceoi. Based on the known clearance mechanism and observed safety profile of bintrafusp alfa monotherapy and standard dose chemotherapy regimens, PK interactions or overlapping toxicities were considered unlikely. Based on this hypothesis, no adjustment in dose selection for chemotherapies was required and bintrafusp alfa 2400 mg Q3W dose was considered optimal for combination studies.

**Conclusions:** 2400 mg Q3W was recommended as the RP2D of bintrafusp alfa for chemotherapy combination studies based on a model-informed drug development approach. Clinical evaluation of this dose is ongoing.

*Proposed INN.

1. Wilkins et al. PAGE 27 2018 abstract 8499
2. Vugmeyster et al. ASCO 2018 abstract 2566

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**T-037**

**Understanding the Fundamentals of PK/PD Index Analysis - Toward a Better Experimental Design and Analysis**

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**Objectives:** PK/PD (pharmacokinetic/pharmacodynamic) index analysis is often used during preclinical research to simplify the PK/PD relationship for a compound to a single PK parameter (C_{max}, AUC, C_{min}) or the percentage of a 24-hour period that the unbound drug concentration exceeds a target threshold (e.g. in vitro EC_{50} or EC_{90}). The objective of the current study is to determine how the half-life of the compound and the PD endpoint affect the results of index analysis.

**Methods:** A set of dose fractionation studies (i.e. same total daily dose delivered QD, BID or TID) covering a range of doses were simulated using two generic PD model structures (direct and indirect response each with a hill equation for the drug effect). The PD endpoint for each simulation was plotted against the four PK metrics (AUC, C_{max}, C_{min}, and time over EC_{50/90}) and the correlation assessed.
**Results.** When the half-life of the compound or the PD endpoint is greater than ~6 hours, all metrics are highly correlated and become indistinguishable. When the half-lives of both the compound and PD endpoint are less than ~6 hours, the \(C_{\text{min}}\) and time over threshold correlate the best with the PD endpoint. Finally, the hill coefficient affects the shape of the relationship but not the selection of PK/PD index.

**Conclusions:** For PK/PD relationships that are described by simple direct and indirect response models, the PK index is related to the half-life of the compound and PD endpoint. Developing a PK/PD model early in the preclinical stage may be beneficial by informing design of preclinical experiments to efficiently elucidate the PK/PD relationship.

**T-039**

**A Population Pharmacokinetic Model Describing Enterohepatic Circulation of Teriflunomide Sodium in Chinese Healthy Volunteers**

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**Objectives:** To quantitatively describe the double-peak phenomenon in pharmacokinetics of teriflunomide sodium (CK8, Cinkate Corporation), a sodium salt of leflunomide active metabolite, to analyze the effects of potential covariates on its PK characters in Chinese healthy volunteers, and to explore the recommended dose for Phase II study in systemic lupus erythematosus (SLE) patients.

**Methods:** An oral relative bioavailability study between teriflunomide sodium tablets and leflunomide tablets was conducted in Chinese healthy volunteers. A total of 30 healthy subjects were enrolled into this random, parallel, open-label study, and 15 subjects orally administered 10 mg leflunomide tablets, the others administrated 10 mg teriflunomide sodium tablets. The PK samples were collected at pre-dose and until 98-day post dose, and the concentrations were determined through validated LC-MS/MS method. A three-compartment model with first-order absorption, first-order elimination and pulsed enterohepatic circulation (EHC) process was established to describe the kinetic characteristics using NONMEM software interfaced with R/PIRANA. EHC was defined as a dynamic parameter to adjust the pulse rhythm of bile excretion. It was assumed that after the subjects had a meal, the maximum value of EHC occurred as 1, and then it declined at first-order rate (K_{ehc}). Additive plus CCV was used as error model to describe the intra-individual variability. Based on base model, we screened the most relevant covariates, including age, sex, body weight, height, body mass index, alanine aminotransferase (ALT), creatinine and genetic polymorphism including BCRP 34G>A, 421C>A et.al using forward selection and backward elimination stepwise method at \(\alpha=0.05\) and \(\alpha=0.01\) (df=1) level. The final population pharmacokinetic (Pop PK) model was evaluated using various diagnostic plots and validated using visual predicted check (VPC) and bootstrap methods. The concentrations after multiple dose of teriflunomide sodium and leflunomide were simulated to support dose optimization.

**Results:** A pulsed EHC PK model was established to estimate PK parameters for both leflunomide and teriflunomide sodium at the same time. Body weight and sex were identified as significant covariates on \(V_c\), BCRP 34G>A gene mutation can significantly increase the CL, and \(K_e\). VPC and bootstrap validation results showed that the developed Pop PK model can successfully capture the major characteristics of the data with acceptable precision. The simulated concentrations after multiple dose of 20 mg leflunomide were comparable with observations in rheumatoid arthritis patients, verifying the model prediction feasibility. The dose regimen of teriflunomide sodium 15 and 25 mg q.d were recommended for Phase II study because the simulated concentrations reached expected effective concentration.

**Conclusions:** An EHC model is optimal to quantitatively describe the pharmacokinetic process of teriflunomide. It is helpful to predict teriflunomide concentration in SLE patients in phase II study and guide dose optimization and safety monitoring.
External validation of pharmacokinetic models for prolonged dexmedetomidine infusion in adult critically ill patients

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Objectives: Dexmedetomidine is an α₂-adrenoceptor agonist used for sedation and anxiolysis in critical care. Pathophysiological changes that result from critical illness may cause considerable changes in pharmacokinetics (PK) (1, 2). We aimed to develop a population PK model based on a critically-ill population, compare prediction accuracies with published models and identify possible covariates that may affect dexmedetomidine PK.

Methods: We included adult patients admitted to our intensive care unit (ICU) expected to require dexmedetomidine infusion for more than 24 hours. Extensive arterial blood samples were drawn at the start, during and after cessation of dexmedetomidine infusion. Plasma was extracted and analyzed. We developed a population-PK model based on measured dexmedetomidine plasma concentrations. Model-based covariate analysis was conducted to evaluate the influence of albumin concentration, severity-of-illness score (APACHE II) and other covariates on key PK parameters. Bayesian approach was used to estimate individual PK parameters based on previously published models. Model-diagnostics and prediction error were compared between our model and previous published models.

Results: The PK of dexmedetomidine in 22 adult ICU patients was best described by a two-compartment linear model. Covariate analysis revealed that peripheral volume of distribution (V2) negatively correlated with plasma albumin concentration. The estimated PK values for elimination clearance, inter-compartmental clearance, central volume of distribution, and V2 were 38.6 (L/h), 114.5 (L/h), 32.1 (L) and 95.1 (L) respectively. The inter-individual variabilities (IIV) associated with above parameters, expressed as coefficient of variation, was 52%, 173%, 127% and 106% respectively. Comparison of prediction performance of our model and other published models are provided in Table 1.

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<th>Models</th>
<th>Base model MDPE (%)</th>
<th>Iirola 2011 MDPE (%)</th>
<th>Iirola 2012 MDPE (%)</th>
<th>Valitalo 2013 MDPE (%)</th>
<th>Smuszkiewicz 2018 MDPE (%)</th>
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Values reported as mean (95% confidence interval). MDPE Median prediction error; MDAPE Median absolute prediction error.

Conclusions: Differences in prediction error between published models appear small. Analysis revealed large IIV associated with the PK parameters of dexmedetomidine in severely ill ICU patients during prolonged infusion, when compared with less sick populations. Correlation between low serum albumin concentration and high V2 was identified. Heterogeneity and inaccuracies seen in pop-PK models may be caused by the varying severity of illness in ICU patients.

Evaluations on the renal function improvement effect of drug A in multiple myeloma patients

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Objectives: Determining the best dosage of drugs in clinical trials and therapies is essential for patients with renal impairment to prevent drug toxicity. Both dedicated PK and population PK studies suggest a dose reduction of drug A in patients with renal impairment. However, one study discovered that drug A could improve the renal function of multiple myeloma patients, which may affect the dosage adjustment during the treatment. Since their using postbaseline renal response is not an accurate variable to determine the overall renal function changes, in this study, we aim to re-evaluate this effect during the drug A treatment period. These results will instruct the dosage administration of this drug to achieve the best efficacy in multiple myeloma patients.

Methods: Two Phase III and placebo-controlled clinical trials of drug A in multiple myeloma patients were identified. We utilized loess regression to visualize the changes of renal functions across the 6-month treatment and conducted Wilcoxon two-sample test to determine the significance of improvement in the entire population or groups with different range of creatinine clearance (CrCL). We further built exponential mechanistic models in NONMEM to quantify the increase and identify related factors.

Results: During the first 6-month treatment, the treatment group significantly elevated more patients’ CrCL level than the placebo group in both studies (Clinical trial 1: p = 0.0001; Clinical trial 2: p = 0.0005). In the 4 groups of patients with different renal function levels (Normal: CrCL >= 90 mL/min; Mild: 60 <= CrCL < 90 mL/min; Moderate: 30 <= CrCL < 60 mL/min; Severe: 15 <= CrCL < 30 mL/min), treatment showed more improvement in the average renal function than placebo. In the exponential mechanistic model to quantify the relationship between CrCL and treatment duration, we determined a positive EMax for treatment relative to the placebo group, indicating the improvement of renal function caused by drug A. Age and body weight were related to the CrCL changes, which is expected because the individual renal function is regulated by these 2 factors. The other variables, such as gender, clinical response and relative change of renal function level, did not display any association.

Conclusions: Drug A could improve the renal function of multiple myeloma patients, and the dosage of it may be needed to adjust during the treatment to achieve the best efficacy in personal medication. Further analysis on more involved factors will help understand the reasons and facilitate the drug A clinical trial designs.

T-042

Elucidating the Disposition of Nano-engineered Mesenchymal Stem Cells using Pharmacokinetic Modeling

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Background: Site-directed delivery of chemotherapeutic agents can improve their therapeutic index by reducing their exposure to non-target tissues. Mesenchymal stem cells (MSCs) possess unique tumor homing capabilities. Our lab is investigating MSCs as cellular carriers for delivering chemotherapeutics selectively to tumors. We have developed novel nano-engineering approaches to load small molecule chemotherapeutic agents such as paclitaxel (PTX) in MSCs. These nano-engineered MSCs demonstrated significantly improved anti-tumor efficacy at 1/10th the dose of conventional PTX therapy. Further, MSC-based delivery mitigated side effects such as leukopenia commonly associated with PTX therapy. In order to understand the complex mechanisms involved in MSC-mediated tumor drug delivery without resorting to expensive animal trials, we pursued a pharmacokinetic (PK)/pharmacodynamic (PD) modeling-based approach. We hypothesized that this approach will serve as a useful guide to help design future clinical trials at optimized doses.
**Objectives:** Our short-term goal was to develop a systematic PK model that can describe tumor disposition of PTX delivered using nano engineered MSCs, with the eventual goal of developing a holistic PK/PD model that will be helpful in successful clinical translation of this novel technology.

**Methods:** A step-by-step approach was used to create a mechanistic PK model for nano engineered MSCs. Plasma and lung concentration-time data from studies conducted using 250 ug/kg equivalent dose of PTX delivered as a solution, nanoparticles, or as nano-engineered MSCs in a lung tumor mice model was used to calculate PK parameters. These parameters were then used to develop a PK model that can describe the in vivo disposition of nano engineered MSCs.

**Results** A mechanistic PK model was developed. Our results suggested that the model is able to describe the PK profiles of PTX delivered by nano engineered MSCs both in plasma and lungs (tumor site) reasonably well. Additional studies are needed to validate the model using predicted dose values of nano engineered MSCs that will result in higher efficacy.

**Conclusions:** A mechanistic PK model was developed for nano engineered MSCs. Future work will focus on developing a PD model using tumor growth inhibition data from efficacy trials. This comprehensive PK-PD model will be used for optimizing dosing regimens for nano-engineered MSCs in preclinical studies.


**T-043**

Weighting for Godot. Is Population Pharmacokinetics in Phase 3 worth the bother?

**Authors:** Daren Austin, Isabelle Pouliquen

**Institutions:** Clinical Pharmacology Modelling & Simulation, G&K given SmithKline

**Objectives:** To evaluate the performance of statistical and pharmacokinetic models to identify exposure covariates using Phase 3 data.

**Methods:** Conventional wisdom holds that population PK parameter (Clearance) estimation from sparse Phase 3 data permits efficient identification of clinical covariates to inform dosing. In this work we challenge this wisdom using data (189 patients, 612 samples) from a Phase 3 clinical trial of a monoclonal antibody dosed subcutaneously. We use linear fixed- and mixed-effects statistical models of log(concentration) to estimate adjusted mean exposure ratios for minimum, maximum and interdecile-range body weights and creatinine clearances compared to median values. We then repeat the analysis using fixed- and mixed-effects one-compartment pharmacokinetic models assuming first-order absorption and elimination with: 1) no covariates, 2) fixed allometry and estimated creatinine clearance effect, 3) estimated allometry and creatinine clearance effect. We evaluate model goodness of fit using Bayes Information Criteria, and model parameter precision using coefficient of variation ($CV = \frac{StdErr}{Estimate}$) for adjusted mean log(exposure ratio). Finally, model efficiency (sample size for precision) is evaluated by analysing 1000 bootstrap trial replicates of sample sizes $2^3$–$10^4$ patients.

**Results:** As expected, fixed-effects models provided better goodness of fit than fixed models, with PK models achieving the lowest overall BIC (Linear (mixed): 772.7 vs. PK (mixed): 668.5). There was, however, no difference in the magnitude of effects between linear statistical and PK models. By contrast, fixed models provided consistently greater precision than mixed models (Linear bodyweight: 16.7% (fixed) vs. 21.8% (mixed), PK bodyweight: 18.8% vs. 26.1%, Linear CRCL: 53% vs. 73.4%, PK CRCL: 57.1% vs. 78.7%), with linear statistical models achieving the highest overall precision (Figure).
Analysis of bootstrap trials with linear statistical and PK models showed no difference in efficiency for bodyweight effects, but √2 more subjects required for PK models to identify creatinine clearance effects.

Conclusions: These results call into question the (ab)use of population pharmacokinetic models to identify clinically important covariates of exposure from sparse Phase 3 data. Conventional statistical models can provide more precise estimates of covariate effects than PK models for the same numbers of subjects, and the use of random effects in both reduces the precision of these estimates. Caution is therefore advised.

“We always find something, eh Didi, to give us the impression we exist?”


T-044

Application of a novel virtual case-matched control (VCMC) approach for benchmarking tumor responses in patients with melanoma treated with pembrolizumab and reduced-dose ipilimumab (KEYNOTE-029) against historical data

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Objectives: Single-arm or non-randomized trials are routinely used for informing Go/No-Go decisions in early oncology development. However, the interpretation of results from these studies can be challenging given their small sample size, variability in follow-up duration, and imbalances in predictive covariates. These biases may be amplified by the traditional RECIST criteria for response and progression, which dichotomizes changes in tumor burden and may lead to erroneous decisions. A modeling and simulation (M&S) strategy utilizing prior clinical data and endpoints based on assessment of continuous tumor dynamics can potentially overcome these limitations. Here, we employ a novel M&S approach, VCMC, to generate in silico control arms with characteristics identical to those of the actual patients in an early-phase study. We demonstrate this approach by generating a virtual pembrolizumab-treated control arm for KEYNOTE-029 Part 1B (a study of pembrolizumab plus reduced-dose ipilimumab for the treatment of advanced melanoma) for comparison against the observed response to combination therapy.

Methods: Previously, a tumor dynamic model for response to pembrolizumab monotherapy in patients with melanoma was developed with data from KEYNOTE-001, -002, and -006. Baseline tumor burden, PD-L1 status, prior ipilimumab treatment, and BRAF mutation status were found to be significant covariates on tumor kinetic
parameters. On KEYNOTE-029 Part 1b, patients with advanced melanoma were treated with 200mg Q3W pembrolizumab and reduced-dose 1mg/kg Q3W ipilimumab (p+i). To generate an *in silico* monotherapy-treated covariate-matched control arm, 1,000 clinical trials were simulated from the estimated variability and uncertainty of the monotherapy model and the actual covariate values from the patients in KEYNOTE-029. Observed and simulated responses were summarized at the last available time-point, and a prediction interval for the response to pembrolizumab monotherapy in this population was generated at various benchmarks (25\textsuperscript{th}, 50\textsuperscript{th}, and 75\textsuperscript{th} percentile of response).

**Results:** Of the 153 patients with melanoma treated with p+i, 139 had ≥ 1 post-baseline scan and were included in the analysis. The 25\textsuperscript{th}, 50\textsuperscript{th}, and 75\textsuperscript{th} percentile of observed responses for the combination therapy were outside the 90% prediction-interval for expected response to pembrolizumab monotherapy in a cohort of matched virtual patients. Subgroup analysis revealed that the 25\textsuperscript{th} and 50\textsuperscript{th} percentile of response in PD-L1 negative patients was better than expected from monotherapy treatment, suggesting that the combination may provide improved responses in this population.

**Conclusions:** VCMC allows for the benchmarking of results from combination studies in a virtual covariate-matched population. The approach revealed a significant improvement in tumor response when pembrolizumab is combined with reduced-dose ipilimumab, regardless of PD-L1 status.


**T-045**

**Optimal paediatric dosing of commonly prescribed essential medicines**

**Authors:** Isabelle Pouliquen, Daren Austin

**Affiliations:** Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline

**Objectives:** To evaluate the dose precision of 161 WHO Essential Medicines for Children and compare recommendations with formally optimal solutions by weight band.

**Methods:** Medicines for children have traditionally been used off-label on a case-by-case basis, but legislation changes have increased focus on paediatric dosing. Although age, bodyweight and organ maturation inform dosing, there is no measure of paediatric dose precision. The extent to which paediatric exposure matches adults therefore remains unknown, together with safety and efficacy implications. We evaluated paediatric dose precision for 161 WHO Essential Medicines for Children (1242 dose recommendations) by estimating the coefficient of variation (CV) of exposure compared to adults. Results were summarised by WHO therapeutic and anti-infective classes and covariates of dose precision explored.

**Results:** Paediatric dose precision for 161 WHO Essential Medicines for Children was 49.0% (95% CI: 43.0–55.8%), with exposure in the range 43–234% of adult. Using the same age and weight recommendations, optimal dose precision was 13.3% (95% CI: 12.3–14.3%), with exposure in the range 79–126%, (i.e., bioequivalent), provided doses were chosen according to our algorithm. Observed dose precision was 3.69 times optimal (95% CI: 3.30–4.13), with only streptomycin and pyrazinamide achieving bioequivalence (Figure). Therapeutic class (by anti-infective class) (P <0.0001), and number of dose adjustments (by administration route) (P = 0.0059) were significant predictors of precision. Toxicity concerns and posology did not influence dose precision (P >0.05).

Weighted mean observed and optimal paediatric dose ratio (ρ, ρ*) and dose precision (CV, CV*) for 161 medicines from the 2017 WHO Model List of Essential Medicines for Children.
Conclusions: Paediatric dosing of WHO Essential Medicines is far from optimal, but bioequivalence with adults is possible with no more than four optimally chosen doses. Evaluation of dose precision can help minimise under- and over-exposure in children, formulate treatment guidelines, test new medicines and evaluate new paediatric drug applications.


T-046

Exposure-efficacy analysis for ribociclib using a variety of exposure metrics

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Objectives: The relationship between survival-based ribociclib efficacy endpoints and several ribociclib exposure metrics was investigated, to support the ribociclib dosing scheme.

Methods: The exposure response (ER) relationship of ribociclib was evaluated in a pooled analysis of three pivotal phase III studies in HR+/HER2- advanced/metastatic breast cancer patients. The association between the various exposure variables and efficacy endpoints (progression-free survival [PFS] and time to tumor response [TTR]) were explored using Cox regression and time dependent Cox regression analyses, in which the exposure was used as a time-varying covariate. Different exposure variables were used in the analyses, including geometric mean Population pharmacokinetics (PopPK) model-predicted ribociclib Ctrough on non-zero dosing days, time varying ribociclib dose intensity (DI) up to the event, and time varying mean PopPK model-predicted ribociclib Ctrough up to the event.
**Results:** The ER analysis for PFS using the time dependent Cox model estimated hazard ratio were close to 1 and/or the 90% CI included 1 using either time-varying mean popPK model-predicted C_{trough} or time-varying DI up to the event. The conventional Cox regression model estimated a hazard ratio slightly higher than one, which could be due to overall exposure metrics not fully reflecting the change in exposure over time in the event of dose reduction or interruption.

**Conclusions:** Based on pooled analysis of three Phase III clinical data, there was no clear relationship between ribociclib exposure and efficacy endpoints, and a definitive conclusion cannot be drawn.

**T-047**

**A Population Pharmacokinetic Model of KPL-716 in Healthy Volunteers and Patients with Atopic Dermatitis**

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**Objectives:** KPL-716, a fully human monoclonal antibody targeting oncostatin M receptor beta (OSMRβ), is under development for multiple chronic pruritic diseases, e.g., prurigo nodularis (PN) and atopic dermatitis (AD). Objectives of the analysis were to 1) characterize the pharmacokinetics (PK) of KPL-716 following intravenous (IV) and subcutaneous (SC) administration in adult healthy volunteers (HV) and subjects with AD, and 2) investigate various SC dosing regimens to optimize practical chronic dosing in a target population.

**Methods:** Single dose data from a Phase Ib clinical study in 57 HV and subjects with AD were analyzed. Most HV and AD subjects received weight-based IV administration (n=24, n=16, respectively; range: 0.3-20 mg/kg), followed by weight-based SC (n=6, n=4; 1.5 mg/kg) and fixed-dose SC (HV, n=7, 360 mg) administration. A non-linear mixed-effects model was developed in NONMEM v7.3. Numerical and visual diagnostics were used to evaluate the model. Simulations were performed using RxODE v0.6.3[1] to explore dosing regimens.

**Results:** The PK of KPL-716 in HV and AD subjects following single-dose IV or SC administration was described using a target-mediated drug disposition (TMDD) model[2] to account for its non-linear clearance. Association and dissociation rate constants were determined experimentally at 0.734 nM-hr⁻¹ and 0.268 hr⁻¹, respectively, and fixed during model development. Relative bioavailability of SC administration in AD was estimated for the model at 65% (based on the comparison of PK of 1.5 mg/kg IV and SC in HV and AD subjects and then revised for dose-dependency based on PK of 360 mg SC in HVs). Body weight was included as a covariate on the central volume of distribution based on allometric theory. A range of simulations was performed to evaluate various SC dosing regimens (Fig 1) using a maximum practical delivered dose of KPL-716 (360 mg in 2mL SC injection). Exposure metrics and time to steady-state were derived for each simulated SC dosing regimen.

**Conclusions:** A KPL-716 population PK model was developed using data from primarily single-dose IV administration and revised on limited single-dose SC data. The model (including TMDD) was used to simulate future efficacy study dosing scenarios for chronic SC dose administration in patients with chronic pruritic diseases in which the target receptor may be upregulated. The maximum deliverable SC weekly dose will support proof-of-concept studies, replicating exposures associated with a prior Early Signal of Efficacy (single high IV dose) and extending them into maintenance dosing. This model also supports determination of practical chronic dose(s)/dosing intervals using a C_{trough} derived from KPL-716 clinical trials.

**References:**

Figure 1. Simulations of various dosing regimens using the final population PK model.
T-048

**PBE and a novel PKPD metric: How to assess regimen equivalence in ADHD therapy?**

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**Objective:** Different methylphenidate (MPH) formulations, immediate release (IR) or extended release (ER), have been developed to treat Attention Deficit/Hyperactivity Disorder (ADHD). With the multiplying possibilities in treatment, we propose an aggregate quantitative metric that aims to effectively compare MPH drug regimens while taking into account a patient’s quality of life, proper choice of dosing times and even combination of formulations.

**Methods:** Within the framework of population pharmacokinetics (PK), we proposed the concept of PK performance scores [1] for the quantitative evaluation of various MPH formulations and simulated therapeutic regimens. Following the FDA guidance on population bioequivalence (PBE), which ensures that two drug products are equivalent in terms of both their mean and variance of Cmax and AUC, we applied PBE’s aggregate criteria to this PK performance score and concluded on regimen equivalence. This proposed approach showed the advantage of comparing regimens with a whole consideration for efficacy, toxicity and tolerance to MPH, which standard PBE metrics cannot as stand-alone measures.

**Results:** Our novel comparison approach was applied to three case studies frequently seen in the treatment of ADHD: (i) Compare a Generic product with the Reference drug, (ii) Switch from b.i.d or t.i.d. of IR MPH to q.d. ER MPH, (iii) Improve the efficacy of a MPH regimen by combining different formulations. Our method proved capable to adequately discern MPH regimens. When PBE was applied with the PK performance score to all of these case studies, our formerly established results on regimen equivalence was correctly concluded: (i) Ritalin IR was indeed equivalent to PMS-IR, (ii) taking once-a-day Concerta might not provide equivalent benefits during the day,
(iii) Combining once-a-day ER and IR formulations might not provide equivalent benefits during the day. Our approach was always in accordance with PBE on Cmax and AUC, but its advantage lies in the joining of these key PK elements.

**Conclusion:** Since our strategy does not limit for fixed doses and formulations but rather any MPH regimen, it provides a computational tool based on M&S that can objectively judge the drug use for patients.


**T-049**

**A Population Pharmacokinetics Analysis of HMS5552, a Novel glucokinase activator, in Chinese T2DM Patients**

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**Objectives:** HMS5552 is a first-in-class novel glucokinase activator which can effectively control both fasting and postprandial glucose, and the phase I and II clinical studies have been completed. In this research we conducted a population pharmacokinetics (PK) modeling analysis to quantify the source of PK variation of HMS5552 in Chinese T2DM patients, so as to provide clinical pharmacological support for the phase III clinical trial design of HMS5552.

**Methods:** Data from the completed phase I and II studies (n=272) were employed for the population PK model. HMS5552 concentrations in plasma were analyzed using nonlinear mixed effects model (NONMEM) method. The model was also used to assess influence of demographic, pathological and physiological characteristics on PK profiles of HMS5552 in Chinese T2DM patients. The final model was diagnosed by goodness-of-fit plots and evaluated by visual predictive check (VPC) method.

**Results:** A two-compartment model with linear absorption and linear elimination was developed to capture PK profile of HMS5552. Typical values of clearance, distribution clearance, central volume of distribution, peripheral volume of distribution, absorption rate constant were 12.6 L/h, 8.29 L/h, 28.3 L, 88.2 L, and 0.432 h⁻¹, respectively. Lean body weight and creatinine clearance were identified to significantly influence the distribution clearance and central clearance, respectively (p < 0.001). However, their clinical effect is minimum and does not require dose adjustment under clinical therapy.

**Conclusions:** The developed population PK model can well capture HMS5552 PK characteristics in Chinese T2DM patients. Covariate analysis indicated that dose adjustment of HMS5552 was not required in the studied patient population.

**T-050**
**Model-Informed Reverse Translational Strategy to Inform the Clinical Pharmacokinetics and First-in-Human Dose Projection of HP1/2: A Humanized Alpha-4-Integrin Antibody.**

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**Objectives:** Reverse translational integration of clinical inputs is important to enhance confidence in predictions. HP1/2 is a recombinant, humanized anti-alpha-4-integrin antibody from the same alpha 4 epitope subclass as Natalizumab (NTZ). This work illustrates how holistic data integration was used to increase predictability and confidence in HP1/2 human pharmacokinetics (PKs) and efficacious dose projections.

**Methods:** Single IV doses of HP1/2 (3 and 30 mg/kg) and NTZ (3 mg/kg) were administered in cynomolgus monkeys (n = 18). A two-compartment model with both linear and Michaelis-Menten eliminations and direct $E_{\text{max}}$ model was used to characterize the PKPD relationship between NTZ and HP1/2 serum concentrations and alpha-4 integrin saturation (receptor occupancy (RO)) in monkeys. HP1/2 human PKs was projected through allometric scaling on monkey PK parameters ($k_{10}$, $k_{12}$, $k_{21}$ and $V_1$) [1]. To ensure adequacy of the approach, a sensitivity analysis was performed using NTZ PK parameters obtained in monkeys and humans by taking the log of the ratio between human and monkey parameters relative to their respective body weight. The inherent monkey parameters were directly applied to human including $K_m$, $V_{\text{max}}$ and the PD parameters ($E_{\text{max}}$, $EC_{50}$, $E_0$ and $V_1$). The $EC_{50}$ of HP1/2 in humans was projected based on data collected in the comparative PKPD study in monkeys, using the in vitro binding affinity ($K_d$) and NTZ $EC_{50}$ in humans [2]. The data were integrated using an empirical scaling approach combining the $EC_{50}$ parameter values obtained in monkeys ($m$) and humans ($h$), after adjusting for potency ($K_d$) differences across species:

$$EC_{50,HP12,h} = EC_{50,NTZ,h} \times \left( \frac{EC_{50,HP12}}{EC_{50,NTZ}} \right)_m \times \left( \frac{K_{d,h}}{K_{d,m}} \right) \times \left( \frac{K_{d,m}}{K_{d,h}} \right)_{NTZ}$$

**Results:** A total of 180 serum concentrations (60 NTZ, 120 HP1/2) and 252 PD (RO) measurements (84 NTZ, 168 HP1/2) were collected. Both HP1/2 and NTZ exhibited a PK profile with target-mediated drug disposition and displayed dose-dependent, RO in monkeys. The $EC_{50}$ value for the formation of drug-bound alpha-4 is projected to be lower for HP1/2 (0.62 µg/mL) when compared to NTZ (2.51 µg/mL [2]) in humans. There was overall good agreement between the predicted and observed NTZ human PK profiles, supporting the adequacy of the allometric scaling approach to project HP1/2 clinical PKs. The MABEL of HP1/2 in human is predicted to be 0.0004 mg/kg (~0.003 mg/kg for NTZ, see Figure 1).

**Conclusions:** Integration of available PKPD data across two humanized anti-alpha-4-integrin antibodies enabled the use of a reverse translational modeling approach for estimating receptor occupancy and human PKs in order to identify a MABEL dose.


**Figure 1. Projected Receptor Occupancy (90% CI) in Human for NTZ and HP1/2**
Modelling the dose-effect relationship between DAV132, an activated charcoal-based product, and fecal concentration of moxifloxacon in healthy volunteers

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Objectives: DAV132 is an oral product which delivers a powerful charcoal-based adsorbent to the late intestine, which reduces fecal concentrations of free MXF in a dose-dependent manner [1,2]. We wished to develop a model of DAV132 effect on fecal fMXF concentration using data of a randomized clinical trial where healthy volunteers received orally MXF alone or with 10 different doses of DAV132.

Methods: A total of 131 volunteers were recruited (Sponsor Da Volterra) and received oral MXF (400 mg OAD) for 5 days alone or associated with various DAV132 doses for 7 days: 0 (no DAV132) 2, 3, 6, 10, 15 and 22.5g/d (2g/d was given BID, 22.5g/d TID, the other doses BID and TID). The previously developed model of plasma and fecal MXF pharmacokinetics was used to characterize the pharmacokinetic properties of MXF and its fecal excretion [3]. Several models accounting for DAV132 kinetics in the gastrointestinal tract were studied. The effect of the amount of charcoal in the distal ileum of the large intestine (called the fecal compartment) in reducing the fecal IMXF was modeled. The analyses were performed using nonlinear mixed effect models and the SAEM in Monolix 2018R2 (Lixoft, France).

Results: Plasma and fecal concentrations of MXF were modeled as in [3] except for adding a diffusion of MXF between the last transit elimination compartment and the fecal compartment. Delivery of DAV132 in fecal compartment was modeled with a transit compartment. Adsorption of fMXF was described with non-linear elimination and the amount of delivered charcoal showed a synergistic effect on adsorption.

Conclusion: The developed model was able to capture the delayed effect of MXF adsorption by charcoal following DAV132 administration and the relationship between DAV132 dose and the reduction in fecal fMXF concentrations.

ENCORE abstract: The results in this abstract have been previously presented in part at PAGE, Stockholm, 11-14th June, 2019 and published in the conference proceedings as abstract PAGE 28 (2019) Abstr 8945 [www.page-meeting.org/?abstract=8945]

T-052

Population pharmacokinetic (PK) analysis of lanreotide autogel® in patients with clinical symptoms associated with inoperable malignant intestinal obstruction

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Objectives: To develop a population pharmacokinetic (PK) model describing the PK characteristics over time of lanreotide autogel® 120 mg in combination with standard of care in the treatment of patients with clinical symptoms associated with Inoperable Malignant Intestinal Obstruction (IMIO).

Methods: Study A-48-52030-269 (IMIO Study) was a Phase II, single-arm, non-randomized, multicentric, prospective and open-label study which aimed to assess the efficacy and safety of lanreotide autogel® plus standard of care in patients with IMIO. Patients were treated with standard of care combined with lanreotide autogel® 120 mg for 28 days. At 28 days, only the patients defined as responders and willing to receive another injection of lanreotide autogel® continued the treatment for an additional 28 days. Sparse pharmacokinetics (PK) samples were collected at 4 timepoints over each dosing interval.

As prior information, a population PK model of lanreotide autogel® in patients with neuroendocrine tumors was available. This NET PK model was assessed and refined until a new model providing an adequate description of the PK characteristics of lanreotide autogel® in IMIO patients was obtained.

Model evaluation included the inspection of goodness-of-fit (GOF) plots and Visual Predictive Checks (VPCs) (1). The population PK analysis was performed using NONMEM software (Version 7.3) (2).

Results: Forty eight patients provided 196 lanreotide autogel® concentrations. The PK of lanreotide autogel® in IMIO patients was adequately described by a three-compartment model with parallel zero- and first-order absorption and a
first-order elimination from the central compartment. This PK model was found to be similar to the structural PK model in the NET population.

The model was parametrized in terms of clearance, volume and absorption constant with lag time. Clearance was 329 L/day and central volume was 9.72 L. Interindividual variability was moderate for clearance, central and peripheral volume, ka, and high for the fraction going through zero order process. The residual error was modeled as an additive term. Model diagnostics for the final population PK model indicated a satisfactory predictive performance after one or two doses of lanreotide autogel®120 ng in patients with IMIO.

**Conclusion:** A population PK model describing the pharmacokinetics of lanreotide autogel® in the IMIO population was developed by considering prior information from the NET population. This model adequately described the data from the IMIO clinical study in patients with inoperable malignant intestinal obstruction.

**References:**


**T-053**

“Novel user-friendly applications for dose individualization of sunitinib and imatinib”

**Authors:** Jonathan Chauvin, Geraldine Ayral, Pauline Traynard

**Affiliations:** Lixoft

**Objectives:** Therapeutic drug monitoring (TMD) and dose individualization can contribute to increased benefits for patients by augmenting the efficacy and/or decreasing the risk of toxicity. TMD is especially interesting for drugs exhibiting a highly variable exposure between patients and a small therapeutic window. Target therapeutic windows are usually defined for the steady state through concentration of repeated dosing regimens and a single drug concentration measurement is made.

While dose individualization has been more and more advocated over the years, the lack of dedicated, user-friendly and reliable decision-support software hampers its use on a large scale in hospital care. We present dose-recommendation tools for two TKIs (sunitinib and imatinib) where clear relationships between exposure and treatment outcome have been established and the associated retrospective results on TMD hospital data.

**Methods:** The dose adaptation procedure is divided in two steps. We first determine the pharmacokinetic parameters of the patient, integrate the information from a population model and the drug concentration measurement(s) to calculate the conditional probability distribution of the individual parameters. Secondly, we use these parameters to perform simulations of alternative doses taking the operational constraints (such as available tablet doses) into account. The dose most likely to reach the target is selected. This procedure has been implemented within two applications: one for sunitinib and one for imatinib in collaboration with hospital clinical pharmacologists.

**Results:** The interface is meant to be usable by non-modelers such as clinicians. The interface allows entering the current treatment, the last dose information. The application returns a dose recommendation as well as the drug concentration profile (and its uncertainty) with the current dose and with the proposed dose. A report is generated automatically and saved to an audit trail local data base.
To evaluate in advance the proportion of the patients that would benefit from sunitinib dose individualization, we have applied our dose-recommendation application to the TMD (without adaptation) database of the Cochin Hospital (Paris, France). The database records around 900 PK measures for 233 cancer patients. For only 16% of the patients the application recommended to maintain the standard dose, while for 67% the recommended dose was below the standard and for the remaining 17% above.

Conclusions: The developed dose-recommendation applications permit to use all available information in a rigorous mathematical framework to suggest the dose most likely to reach the therapeutic target. In addition, estimating the individual parameters gives more flexibility not requiring the measurement being at the trough. The retrospective study on past sunitinib data shows the need for TMD and dose adaptation. In addition, the dose adaptation is expected to reduce the overall cost of the treatment as the average recommended dose is smaller than the standard dose.

T-054

Population pharmacokinetic model of lanreotide autogel® in Chinese patients with acromegaly

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Objectives: To performa population PK analysis of lanreotide autogel® concentration data from the LANTERN study using non-linear mixed-effects modelling.

Methods: LANTERN (NCT02493517) was a phase 3, open-label study comparing the efficacy and safety of lanreotide autogel® 60, 90 or 120 mg with lanreotide 40 mg prolonged release (PR) in Chinese patients with active acromegaly. A population PK model was previously developed in the non-Chinese population with acromegaly. The model was a 3-compartment model with parallel zero and first-order absorption and a first-order elimination from the central compartment.

In a first step, the previously developed lanreotide population PK model in a non-Chinese population was used to describe the data from LANTERN study and to check for potential bias.

In case the previously proposed lanreotide population PK model was not able to adequately describe data from LANTERN study, then this PK model was planned to be further developed.

Model evaluation included the inspection of goodness-of-fit (GOF) plots and Visual Predictive Checks (VPCs) (1). The population PK analysis was performed using NONMEM (Version 7.3) and the first order conditional estimation method with Interaction (2).

Results: The analysis dataset comprised 64 patients providing 742 lanreotide concentrations. Evaluation of the GOF plots and the distribution of residuals showed some trends with time and prediction, which indicates that specific PK parameters needed to be re-estimated. Lanreotide clearance was estimated to be 424 L/day for a male or female Chinese patient of 70 kg as compared with 592 L/day in a 70 kg non-Chinese patient. The absorption profile was characterized by a duration of the zero-order process of 1.95 day and a first-order absorption rate of 0.0171 and 0.0223 day⁻¹ in females and males, respectively. Overall a 30% decrease in apparent clearance value was observed for a 70 kg Chinese male patient with acromegaly as compared with a 70 kg non-Chinese patient. The first order rate constant ka and the fraction undergoing the first order process (F2) were 2.8-fold and 1.6-fold higher in the Chinese population respectively.

Evaluation of the GOF plots and VPCs indicated that the predictions from the final lanreotide population PK model matched reasonably well with the observed data of LANTERN study.

Conclusion: A population PK model describing the pharmacokinetics of lanreotide autogel® in the Chinese population with acromegaly was developed by considering prior information from the non-Chinese population. This model adequately described the data from the clinical study in Chinese patients with acromegaly.

References
Exposure-Response Model of Subcutaneous C1-Inhibitor Concentrate to Estimate the Risk of Attacks in Patients with Hereditary Angioedema using Data from the COMPACT Phase III and Open-Label Extension Studies

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Objectives: Hereditary angioedema (HAE) is a rare, debilitating, and potentially life-threatening genetic disease caused by a deficiency in functional C1 esterase inhibitor (C1-INH). Long-term prophylactic administration of subcutaneous C1-INH (C1-INH [SC]) is an established treatment option for patients with HAE. Previously, data from the COMPACT Phase III study informed a population pharmacokinetic (PK) model of trough C1-INH functional activity (C1-INH[f]) following C1-INH (SC) administration.¹ An exposure-response (ER) model was also previously developed with data from the COMPACT Phase III study to characterize the relationship between C1-INH(f) and the risk of an HAE attack.² This study aims to assess the relationship between C1-INH(f) and risk of attacks in patients with HAE using data from the COMPACT open-label extension (OLE) study (NCT02316353) in addition to the COMPACT Phase III (NCT01912456) data that were used to develop the previous model.

Methods: Data from the COMPACT OLE study were used to update the previously developed repeated time-to-event model, to characterize the frequency and timing of HAE attacks as a function of C1-INH(f), and confirm the relationship between C1-INH(f) and the risk of an HAE attack. An exploratory ER evaluation was performed to determine if there were differences in the effect of C1-INH (SC) administration on the number of HAE attacks between study populations, specifically: patients enrolled in the COMPACT Phase III trial, C1-INH (SC)-naïve subjects in the OLE study, and patients who crossed over to the from the COMPACT Phase III to OLE study. The final model was used to simulate the absolute hazard of attacks over a wide range of C1-INH(f) values (20–120%). The hazard ratio was computed using the geometric mean of observed baseline C1-INH(f) as the reference, compared to C1-INH(f) ranging from the reference to 120%.

Results: The final ER model, updated with additional data from the COMPACT OLE study, included a baseline hazard and non-linear drug effect. The subpopulations identified were evaluated as categorical covariates on baseline hazard in the ER analysis. Exploratory analysis showed that the C1-INH (SC) drug effect was the same across study subpopulations but suggested that there may be differences in baseline HAE attacks across study subpopulations. The drug-effect parameters, EC₅₀ and Eₘₐₓ, were estimated to be similar to the previous analysis.²

Conclusions: Inclusion of data from the COMPACT OLE study in addition to the COMPACT Phase III data confirms that the previously developed time-to-event model adequately describes the relationship between C1-INH(f) and both the timing and frequency of HAE attacks. The ER model can characterise the relationship between C1-INH(f) and HAE attack risk in the OLE study.

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Objectives: LC51-0255, a novel selective sphingosine-1-phosphate 1 (S1P1) receptor modulator, is under development by LG Chem, Ltd. to treat inflammatory diseases such as ulcerative colitis (UC). Expected mechanism of its anti-inflammatory effect is to sequester lymphocytes to secondary lymphoid organs. Since excessive exposure to S1P1 modulator may increase the risk of infective disease as well as cardiovascular/pulmonary adverse events, appropriate prediction of pharmacokinetic (PK) profile can contribute to safety of patients. Current study aims to develop a population pharmacokinetic model for LC51-0255 in healthy Korean male subjects.

Methods: A population pharmacokinetic model for LC51-0255 was used to develop a nonlinear mixed-effects method in NONMEM (version 7.4). A total of 829 plasma LC51-0255 concentration from 40 subjects (8 subjects in each dose group; 0.25, 0.5, 1, 2, and 4 mg) participated in a phase I single ascending dose pharmacokinetic study were used in construction of base population pharmacokinetics model. Number of compartments, absorption kinetics (zero-order/first order/lag time), linear/nonlinear elimination kinetics and covariates of were assessed to identify the model that best describes pharmacokinetic profile of LC51-0255. Performance of the model was evaluated with basic goodness-of-fit diagnostics and visual predictive checks.

Results: A two-compartment linear pharmacokinetic model with first-order absorption and first-order elimination well described pharmacokinetic profile of LC51-0255. The typical estimates of clearance (CL), central volume of distribution (V2), peripheral volume of distribution (V3), intercompartmental clearance (Q) and absorption constant (Ka) was 1.32 L/h, 113 L, 50.7 L, 5.05 L/h, and 0.891 /h, respectively. The inter-individual variability (CV%) of CL, V2, V3, Q and Ka was 21.3 %, 19.1 %, 28.8 %, 48.5 %, and 65.7 %, respectively. Model evaluation by visual predictive checks suggested that the proposed model was adequate and robust with good precision.

Conclusions: The population pharmacokinetic model for LC51-0255 properly described the observed data, suggesting potential for utilization in further clinical trials.

T-057

Sex-specific Computational Models for Blood Pressure Regulation in the Rat

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Objectives: Renal hemodynamics play a critical role in blood pressure regulation, while renal autoregulatory mechanisms maintain kidney function for varying blood pressure. Computational models have been developed of the cardiovascular system to simulate blood pressure regulation in humans, including the seminal model by Guyton, et al. [1]. Although the Guyton model and its many variants represent mechanisms for renal autoregulation, they fail to adequately maintain glomerular filtration rate for a sufficiently wide range of blood pressure. Additionally, while such human models have clinical value in that they can be used to assess the effects and reveal the mechanisms of hypertensive therapeutic treatments, rodent models would be more useful in assisting the interpretation of animal experiments. Finally, despite well-known sexual dimorphism in blood pressure regulation, all published models are
gender neutral. Given these observations, the goal of this work is to develop the first sex-specific computational model of blood pressure regulation for the rat.

**Methods**: The resulting model represents the interplay between cardiovascular function, renal hemodynamics, and kidney function. It also includes the actions of the renal sympathetic nerve activity and the renin-angiotensin-aldosterone system. The model was developed by using rat data to reparametrize human quantities, renal perfusion experiments to calibrate autoregulation, and angiotensin II infusion experiments to validate. A hypertensive virtual rat was then created by perturbing the model away from baseline based upon typical symptoms of hypertension. Finally, the model was applied to investigate the cardiovascular effects of antihypertensive treatments and renal effects of drug combinations.

**Results**: A sex-specific computational model of blood pressure regulation for the rat was developed. The model autoregulates blood pressure and renal function under physiological perturbations. The model was applied on a virtual hypertensive rat to investigate the cardiovascular effects of antihypertensive treatments including diuretics, angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), as well as nonsteroidal anti-inflammatory drugs (NSAIDs). Simulations were also conducted to identify risk factors for acute kidney injury following the administration of a combination of these drugs.

**Conclusions**: The first sex-specific computational model of blood pressure regulation for the rat was developed, thus creating an in-silico framework to study hypertension in rodent experiments tailored to each gender. It autoregulates both blood pressure and renal function. Model simulations suggested effective antihypertensive treatment strategies, as well as identified risk factors for acute kidney injury following the administration of a combination of these drugs.

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**T-058**

**Generalized Population Modeling, a Pharmacometrics Paradigm for Integrating Machine Learning Algorithms: A Case Study of Insulin Related Metabolomic Biomarkers in Mexican Americans**

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**Objectives**: There is an unmet need for identifying innovative machine learning (ML) strategies for pharmacokinetics and pharmacodynamics (PK/PD) and pharmacometrics applications. We investigate Generalized Population Modeling (GPM), a novel paradigm that integrates ML algorithms, PK/PD structural models, non-linear mixed effects models, and “big data”. We hypothesize that GPM will enhance forecasting of drug outcomes in under-represented populations. We assessed random forest regression (RFR) in conjunction with Bayesian networks (BN) for the ML component of GPM. The utility of GPM for predicting cholesterol dynamics in Mexican-Americans was assessed.

**Methods**: The performance of the ML methods was evaluated using simulation experiments. The case study focused on the interactions between metabolism and cholesterol dynamics in humans. The NHANES 2007-2008 dataset was used as a population-based external dataset for enabling the ML component of GPM. RFR and BN analyses were implemented using the `randomForestSRC` and `bnlearn` R packages. Relevant individual-specific factors were identified using variable importance (VIMP) and minimal depth (MD). Cholesterol dynamics in humans was characterized by a two-compartment model with cholesterol production rate (PR), central (M1) and peripheral (M2) pool sizes.

**Results**: Simulation experiments evaluated the sensitivity, specificity and ordinal classification of the RFR and BN suite of ML methods in GPM. In the case study, GPM was utilized to identify subject-specific factors associated with cholesterol dynamics and insulin sensitivity in Mexican-Americans. Cholesterol homeostasis covariate models (BIC_{covariate}=2099, BIC_{base}=2110) were evaluated using FOCEI NLME (NONMEM 7.4.1). Insulin resistance was assessed with the Homeostasis Model Assessment (HOMA2) (1). Mexican-Americans had greater insulin resistance...
compared to Other Hispanic \( (p < 0.1) \), White \( (p < 0.0001) \), Black \( (p < 0.0005) \) and Other Race \( (p < 0.005) \). The multivariate-RFR prioritized all 611 relevant variables using VIMP and MD. The complex conditional dependencies of the top 10 relevant and cholesterol homeostasis variables were evaluated using the BN (Figure 1). The BN identified the inter-dependencies between glucose, insulin, uric acid, blood cadmium with cholesterol production rate. Interestingly, the associations of cadmium and uric acid levels with the cholesterol pathway are emerging from other independent metabolomic investigations.

**Conclusions:** GPM identified biologically plausible relationships between cholesterol production rate and insulin, and glucose and peripheral cholesterol pool size in the BN. These results are concordant with dependencies identified in Mexican Americans in the emerging clinical metabolism literature (2). Our results demonstrate the potential utility of GPM to inform and enhance pharmacometric modeling.

Multiscale model identifies optimal schedule for treatment of Acute Myeloid Leukemia in vitro with MCL1 inhibitor AZD5991
Incorporation of a time-dependent loss mechanism into the delay process

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Objectives: The distributed delay approach provides an alternative and flexible way to model delayed outcomes in PKPD studies, and it does not suffer the disadvantages of the traditional transit-compartment-model (TCM) approach [1]. It involves convolution of the signal to be delayed ($S$) and the probability density function (PDF) ($g$) of the delay time, $S(t) = \int_0^{\infty} g(\tau)S(t - \tau)d\tau$. Due to its inherent assumption, the distributed delay approach
cannot be used to model delayed outcomes involving loss mechanism (e.g., degradation, emigration) during the delay process. To partially achieve this, the distributed delay approach was extended in [2] to incorporate a constant loss mechanism into the delay process. Wherein it was found that the loss may have a significant effect on the mean delay time as well as its variance. The goal here is to demonstrate how to further extend the distributed approach to incorporate a time-dependent loss mechanism into the delay process.

**Methods:** Assume that the loss of mediators (e.g., cells, drug molecules) occurs at a first-order time-dependent rate \( \kappa_1 \). Then the number of mediators at \( \tau \) time ago that survive to time \( t \) is given by \( \exp \left( - \int_{t-\tau}^{t} \kappa_1 (\xi) d\xi \right) S(t - \tau) \). Hence, the delayed outcome is described by \( S(t) = \int_{0}^{\infty} g(\tau) \exp \left( - \int_{t-\tau}^{t} \kappa_1 (\xi) d\xi \right) S(t - \tau) d\tau \).

**Results:** Due to the time-dependent loss, the delay time for the survived mediators is a random process instead of a random variable with PDF at time \( t \) given by \( g_1(t, \tau) = \frac{g(\tau) \exp \left( - \int_{t-\tau}^{t} \kappa_1 (\xi) d\xi \right)}{\int_{0}^{\infty} g(\tau) \exp \left( - \int_{t-\tau}^{t} \kappa_1 (\xi) d\xi \right) d\tau} \). Similar to the distributed delay approach without loss, if \( g \) satisfies certain conditions, then the distributed delay with time-dependent loss can be reduced to a system of ODEs. For example, if \( g \) is the PDF of an Erlang distribution, then it reduces to an extended TCM with time-dependent loss rate incorporated as shown in Figure 1, which includes the model for describing the slow mineralization of bone in [3] as a special case (where \( \kappa_1 \) denotes the resorption rate, and is affected by both disease progression and drug effect).

**Conclusions:** The distributed delay with time-dependent loss provides a more general and realistic description of the delay process, and hence may capture more complex features than the one either without loss or with a constant loss.


**T-061**

**Single Objective Genetic Algorithm Based Approach for Optimal Population Pharmacokinetic/Pharmacodynamic (PK/PD) Model Selection for Clinical Trial Data Associated with Schizophrenia**

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Objectives: Typically, population PK/PD model selection utilizes a stepwise approach identifying the structural model followed by covariate and statistical models. This approach ignores the effect of interaction between the structural, covariate and statistical components of the model and may result in a locally optimal instead of a globally optimal model. A full model backward elimination approach has been suggested as a means of identifying the model while avoiding some of these issues (FFEM) [1] but with shortcomings [2]. A Genetic Algorithm (GA) approach may be a potential solution to the issue of model selection that addresses these issues. The work compares the model identified using single objective GA (SOGA) [3] approach that identified with backward elimination.

Methods: A double blinded, phase 1b/2a clinical trial was conducted to evaluate the effects of the selective estrogen receptor beta agonist (LY500307) in Schizophrenia patients. Linear mixed effect models were developed using NONMEM 7.4 to capture the effects of treatment time on the change of selected clinical endpoints over time. The stepwise approach began with the full model including both drug effect and placebo effect. Each effect was removed from the full model singly and the change in OFV was evaluated with the likelihood ratio test. Non-significant effects were removed from the model. The final model is the one with no more non-significant effect.

With SOGA, a fitness function was used to guide the model selection:

\[ \text{Fitness} = -2LL + 2 \cdot N_{\text{par}} + 10 \cdot P_{\text{converge}} + 10 \cdot P_{\text{covariance}} \]

where \(-2LL\) is the negative 2 log likelihood, \(N_{\text{par}}\) is the number of estimated parameters, \(P_{\text{converge}}\) is penalty for unsuccessful convergence and \(P_{\text{covariance}}\) is a penalty for an unsuccessful covariance step.

Results: The model obtained using full model backward elimination approach for MCCB-composite (cognition) score had an OFV value of 1350.601 and for NSA-Total (negative symptoms) score the OFV value was 2388.148. The OFV value of the model selected using GA for MCCB-composite score had an OFV value of 1350.601 and for NSA-Total score had an OFV value of 2375.77.

Conclusions: SOGA was able to identify a model that had an OFV that was equal to or lower than that of the model selected by traditional approach. At the same time, the SOGA approach automated the model development/selection process thereby helping the researchers to focus on model evaluation, interpretation and hypothesis testing rather than on manual editing of control streams.


T-062

LikelihoodProfiler Is a Software Package for Practical Identifiability Analysis for the Large-Scale Dynamic Models

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Objectives: The reliability and predictability of a quantitative systems pharmacology (QSP) model depends on the calibration of model parameters. Experimental data can be insufficient to identify all the parameters unambiguously and “confidence intervals” are used to express parameters identifiability or to state “non-identifiable” cases (with unbounded confidence intervals). Currently the practical identifiability analysis [1] in QSP modeling is limited due
to computationally expensive operation of likelihood profile (LP) scan. We developed a series of fast and robust algorithms integrated in the LikelihoodProfiler software package which evaluate confidence intervals and perform identifiability analysis more efficiently than the previously published methods.

**Methods:** The presented package includes the original "one-pass" algorithm named CICO (Confidence Intervals evaluation by Constrained Optimization), which utilizes the Inequality-based Constrained Optimization for efficient determination of confidence intervals and detection of "non-identifiable" parameters for complex QSP models. The new package version (v0.2) also includes two "multi-pass" algorithms which uses interpolation (linear and quadratic) to optimize LP scan by reducing number of LP calls. The developed methods utilize the nonlinear optimization algorithms implemented in NLopt library [2]. The software package is written in Julia language [3] and has been registered in Julia repository.

**Results:** CICO translates confidence intervals estimation problem into an optimization problem and addresses the main disadvantages and restrictions of the “multi-pass” algorithms. Being an optimization algorithm it makes less intermediate likelihood evaluations in comparison with “multi-pass” algorithms which results in performance enhancement. The algorithms were tested on the complex model from DREAM challenge [4] and compared with Matlab Data2Dynamics package which uses a “multi-pass” algorithm. The comparison demonstrated that the new methods required from 10 to 500 times less profile function calls in comparison to Data2Dynamics approach to have comparable results. The package is distributed under MIT free license and available on GitHub [5].

**Conclusions:** We have developed a set of algorithms to perform practical identifiability analysis and confidence intervals evaluation using PL method which can be applicable for practical use. The CICO algorithms is efficient for complex QSP models where each likelihood evaluation can be computationally expensive and some parameters are non-identifiable.

*The results in this abstract have been previously presented in part at ICSB 2018, Lyon France, October 2018 and published in the conference proceedings.*

**References:**

5. LikelihoodProfiler is a Julia package for identifiability analysis, https://github.com/insysbio/LikelihoodProfiler.jl

**T-063**

**OptiDose: Computing the optimal individual dosing regimen with constraints on model states to include side effects**

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**Objectives:** Previously, we developed and validated an optimal dosing algorithm (OptiDose) to solve an optimal control problem (OCP) that computes the optimal individualized dosing regimen for PKPD models [1]. This method is now extended to include constraints on model states, so-called state constraints, e.g. to control side effects such as myelosuppression (decrease of blood cell production) in anti-cancer treatment.
Methods: To formulate the finite dimensional OCP two objective functions are combined to a so-called penalty function. The first objective function quantifies the difference between the desired disease state progression and the actual state generated by the treatment. The second additional objective function measures the violation of the state constraints. Then, the optimal (while satisfying the state constraints) individual doses are computed by solving the OCP with a gradient-based descent algorithm, e.g. a sequential quadratic programming method [2].

Results: Our OptiDose algorithm was extended with state constraints and implemented in Matlab. For application, a large PKPD model consisting of a tumor growth inhibition part [3] and a myelosuppression part [4] was constructed. For a desired tumor weight progression, the optimal individual doses were computed while assuring that the amount of neutrophils stays above a pre-defined threshold. We observed that state constraints since they hold over large parts of the observation horizon are numerically more challenging than e.g. restrictions on the doses only [2]. For random initial dosing guesses slightly, different optimal solutions were computed. Some solutions kept the tumor weight closer to the reference while allowing minimal drops below the neutrophil threshold, whereas others enforced the state constraint more strictly alongside larger deviations to the tumor reference weight.

Conclusion: To compute the clinically relevant optimal individual doses, it is essential to include possible side effects in the PKPD model and consequently in the optimization process although these state constraints lead to numerically much harder problems.


T-064

Application of a tumor penetration model for the prediction of tumor target engagement and dose justification

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Objectives: Immunoncology (I/O) is the main emphasis of oncology drug development and large molecules make up a large fraction of new drug candidates. Optimal dose selection is a key decision in early clinical oncology to balance efficacy and safety. Instead of choosing maximum tolerated/administered dose (MTD/MAD), quantitative characterization of the pharmacology of I/O mAbs can aid optimal dose selection. Target engagement (TE) on T-cells is the first step driving the pharmacology of I/O mAbs. Hence, the dose of I/O mAbs can be informed by TE. A key challenge in the intra-tumoral characterization of TE is obtaining tumor biopsies. To fill this gap, physiologically based pharmacokinetic (PBPK) model can integrate knowledge of mAb distribution and receptor properties to predict intra-tumor TE. Incorporating the dynamic interaction between an antibody and its target (i.e., TMDD) within a PBPK model framework enables quantitative prediction of dose needed for targets saturation within tumors.

Methods: Antibody minimal PBPK model, previously developed by Cao et al (Cao, Balthasar et al. 2013), was adapted for pembrolizumab. A tumor compartment based on antibody PBPK model published by Baxter et al is incorporated in the minimal PBPK model (Baxter, Zhu et al. 1995). In addition, spatial heterogeneity of tumor is modeled by applying a spherical tumor model developed in the Balthasar’s lab (Abuqayyas 2012). Simulations were performed to predict PD-1 engagement in vascularized and different layers of necrotic regions of tumor. Additionally, impact of higher PD-1 expression on tumor PD-1 engagement was simulated.
**Results:** Simulations suggest that 200 mg pembrolizumab is required to achieve PD-1 saturation, supporting 200 mg as an optimal dose. Furthermore, simulation demonstrates that 400 mg Q6W regimen can sufficiently saturate PD-1 in tumor, supporting the switch from 200 mg Q3W to 400 mg Q6W pembrolizumab dosing regimen.

**Conclusions:** PBPK model, incorporating tumor physiology, physiological data available in the literature, as well as clinical PK data can be used to predict intra-tumor TE, when experimental measurements of antibody concentration and TE in tumor are insufficient/lacking. PBPK model predictions can be used for optimal dose selection of I/O mAbs.


**T-065**

**Impact of Partition Coefficient Prediction Methods on PBPK Model Output Using a Unified Tissue Composition**

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**Objectives:** Tissue:plasma partition coefficients are critical parameters in physiologically-based pharmacokinetic (PBPK) models, yet the coefficients are challenging to measure *in vivo*. Several mechanistic-based methods have been developed to calculate partition coefficients using tissue composition information and the compound’s physicochemical properties. However, the impact of using different methods on model predictions was not adequately quantified. Furthermore, the inconsistency in the tissue composition information used by each method adds another level of complexity that needs to be sorted out before a reliable comparison between the methods can be assessed.

**Methods:** This study proposed a unified tissue composition for humans that was used as input for five common calculation methods. The methods were implemented in R and were used to calculate partition coefficients for 11 drugs, classified as strong bases (metoprolol and caffeine), weak bases (voriconazole, alfentanil, nevirapine, and midazolam), acids (thiopental and nifedipine), neutrals (digoxin and artemether), and zwitterions (ofloxacin). PBPK models were developed for each drug using the open-source R package mrgsolve. PBPK model predictions using each partition coefficient method were then compared to observed plasma concentrations for each drug. The accuracy of each PBPK model output was assessed using the relative RMSE, AUC error, and half-life error. Monte Carlo simulations were used to investigate the impact of interindividual variability in tissue composition values and physicochemical parameter uncertainty on PBPK model output using each partition coefficient method for voriconazole.

**Results:** The developed tissue composition database was implemented in all calculation methods, and the resulting partition coefficients showed acceptable correlations with those predicted using the reference tissue compositions (PCC range for human reference tissue compositions: 0.80 - 1.00). The analysis highlighted the importance of using a unified tissue composition for reliable comparison between the partition coefficient calculation methods and that no single one of these methods consistently yielded the most accurate PBPK model output. For example, the alfentanil relative RMSE ranged between 0.453 and 0.531, AUC error ranged between 0.014 and 0.080, and half-life error ranged between -9.964 and -0.259. The errors for the other drugs were comparable to those for alfentanil, except a few outliers. In particular, a relative RMSE for nifedipine was 12.702, and a half-life error for nevirapine was -343.280. The analysis also showed the relatively large impact of interindividual variability and physicochemical uncertainty on partition coefficient predictions, and, hence, on the PBPK model output.
Conclusions: PBPK model outputs using all partition coefficient methods should be considered during drug development, and a partition coefficient method may be selected as part of the model optimization process. The impact of interindividual variability and physicochemical uncertainty should be considered when choosing a partition coefficient method during PBPK model construction.

T-066

A Physiologically Based Pharmacokinetic Model of Vismodegib: Deconvoluting the Impact of Saturable Plasma Protein Binding, pH-dependent Solubility and Nonsink Permeation

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Objectives: Vismodegib is a Hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery or radiation. Vismodegib is a metabolically stable, BCS class II compound that displays unique PK characteristics including saturable protein binding to alpha-1 acid glycoprotein (AAG) and apparent time-dependent bioavailability leading to non-linear PK with time and dose, significantly faster time to steady-state and lower than predicted accumulation (1,2). Given these unique characteristics, a PBPK model was developed to explore mechanistic insights into saturable protein binding and complex oral absorption processes and deconvolute the impact of these independent non-linear processes on vismodegib exposure.

Methods: Simcyp V18 was used for model development. Dissolution was characterized using the diffusion layer model (DLM) with observed intrinsic solubility and particle size distribution. Oral absorption was characterized using the multi-layer gut wall (M-ADAM) model and mechanistic permeability (MechPeff) model, incorporating transport across an Unstirred Boundary Layer (UBL) compartment between the luminal fluid and enterocyte in each segment of the gastrointestinal tract. A minimal PBPK distribution model was utilized with saturable protein binding modeled using concentration dependent KD values for AAG and albumin. PBPK simulations were compared with observed PK data from clinical trials in healthy subjects and oncology patients (2).

Results: A saturable protein binding model incorporating high affinity binding to AAG (KD 0.05 µM) and low affinity binding to albumin (KD 35 µM) accurately simulated vismodegib total and unbound exposure observed in oncology and healthy volunteer studies. Saturation of vismodegib protein binding led to substantially lower total drug accumulation, time to steady-state and Css total; for unbound exposure, Css unbound and accumulation were unchanged, but time to steady-state was reduced. Vismodegib oral absorption occurred mainly in the small intestine (64%), with a substantial large intestine component (36%). Due to slow systemic CL in combination with low, pH-dependent solubility in the GI lumen, the concentration gradient driving oral absorption declined with multiple doses, leading to a 32% decrease in vismodegib fraction absorbed (fA) from single dose to steady-state. Fed simulations suggested that increased solubility and dissolution is partially offset by reduced permeability across the UBL due to slower diffusion of micelle-bound drug.

Conclusions: The unique PK properties of vismodegib can be explained by a combination of saturable protein binding and complex oral absorption involving low and pH-dependent solubility, dissolution and nonsink permeation through PBPK modeling.


T-067

Aging does not impact the magnitude of drug-drug interactions – a proof of concept study using physiologically based pharmacokinetic modelling
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Objectives: Aging is characterized by physiological changes which have an impact on drug pharmacokinetics [1], however, only a limited number of drug-drug interactions (DDIs) have been studied in the elderly. The aim of this proof of concept study was to investigate the impact of aging on DDI magnitudes through physiologically based pharmacokinetic (PBPK) modelling.

Methods: A whole-body PBPK model constructed in Matlab® 2017a was used [2] considering age-related physiological changes [3]. Two DDIs involving midazolam were studied: I) in combination with clarithromycin and II) with rifampicin. Simulations were firstly carried out in young adults (20-40 years), before predicting drug disposition in the elderly (66-80 years) without modifying drug parameters. Simulations were compared to clinically observed data for both drug combinations to ensure correct predictions [4-6]. DDI magnitudes were predicted across adulthood (20-99 years) in 100 virtual individuals (50% women) in 16 age groups and the area under the curve (AUC) ratio was normalized to the youngest investigated age group (20-24 years).

Results: Simulated concentration-time profiles and predicted DDI magnitudes were within 1.5-fold of clinically observed data [4-6] for both drug combinations and age groups (Table 1). The PBPK model suggested no change in DDI magnitudes with advanced age for both investigated drug combinations.

Conclusions: Aging neither alters inhibition (clarithromycin) nor induction (rifampicin) of midazolam. Age-related physiological changes impact victim drugs and inhibitors/inducers to the same extent thereby leading to unchanged DDI magnitudes. Thus, prediction of the PBPK model suggest a similar management of DDIs in the elderly compared to young adults.

Table 1:

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Young Adults</th>
<th>Elderly Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam + Clarithromycin</td>
<td>7.50 ± 5.50</td>
<td>7.54 ± 6.77</td>
</tr>
<tr>
<td>Midazolam + Rifampicin</td>
<td>0.10 ± 0.09</td>
<td>0.10 ± 0.09</td>
</tr>
</tbody>
</table>


T-068

Model-informed Drug Development Using PBPK Modeling and Simulations: Glibenclamide following Intravenous Administration
Objectives: Glibenclamide (GLB) is globally approved for the treatment of diabetes as an oral formulation and its intravenous (IV) administration is under development for severe cerebral edema secondary to large hemispheric infarction, a form of ischemic stroke. GLB is extensively metabolized by CYP3A4 and 2C9, with OATP1B1 uptake transport proposed to be the rate limiting step in its hepatic disposition. Based on oral GLB data, physiologically-based pharmacokinetics (PBPK) modeling and simulations (M&S) were performed to predict GLB PK and metabolic and transporter-mediated drug-drug interaction (DDI) potentials, assess the impact of CYP2C9 genetic polymorphism and inter-ethnic difference between Chinese and Caucasians, following IV administration.

Methods: All M&S were conducted in Simcyp® and models were evaluated based on comparison of predicted vs observed data, and recovery of oral GLB DDIs (<25% difference from clinical observations). An apparent in vitro-in vivo disconnect in the contribution of CYP isozymes to GLB metabolism has been noted, particularly for CYP2C9. Sensitivity analysis showed fraction metabolized (fm) >0.9 is needed to recover the clinical impact of CYP2C9 genotype on GLB PK. Therefore, two final full PBPK models incorporating fm of 0.3 (supported by in vitro data) or 0.9 for CYP2C9 were carried forward to project the worst-case scenarios for IV GLB metabolic DDI. For all simulations conducted in Chinese, the Simcyp database constructed based on demographic data of 8118 Han Chinese was used.

Results: The predicted GLB PK (oral or IV administration) and associated DDIs were in close agreement with clinically observed data. IV GLB C_{max} and AUC were predicted to change by 6%-26% and 9%-22% under potent inhibition or induction of CYP3A4 or CYP2C9 (itraconazole, IV fluconazole and rifampin), respectively. Potent inhibition of OATP1B1 (IV rifampin) increased IV GLB C_{max} and AUC by ~40% and ~13%, respectively. Comparison of GLB exposures between CYP2C9 poor metabolizers (CYP2C9 *1/*2 and *1/*3) and wildtype (CYP2C9 *1/*1) showed increased C_{max} and AUC by 71% and 121%, respectively. Following either oral or IV GLB administration, ≤20% difference in GLB exposure was observed between Chinese and Caucasians.

Conclusions: PBPK strategy and framework were used to successfully assess the relative bioavailability of GLB following different routes of administration (oral vs. IV), demonstrate low DDI risk associated IV GLB under metabolic or transporter modulations, evaluate the impact of CYP2C9 genetic polymorphism and establish minimal inter-ethnic variation between Chinese and Caucasians. Quantitative prediction of GLB systemic exposures using PBPK M&S provides essential understanding on dosing recommendation in different sub-populations, and critical guidance on mode-informed drug development.

T-069

Assessing factors influencing tumor delivery efficiency of nanoparticles in tumor-bearing mice using a physiologically based pharmacokinetic modeling and simulation approach

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Objectives: Engineered nanoparticles or nanomaterials (NPs or NMs) have been applied in many biomedical fields for diagnosis and targeting therapy of various diseases, including cancer. However, translation of NP-based drug into clinical applications is limited partly due to low delivery efficiency to the tumor and lack of knowledge on the quantitative effects of various physicochemical factors on NP tissue/tumor distribution [1]. The goal of this study was to determine the main factors that affect tumor delivery efficiency of NPs and to identify the relative contributions of different factors using a physiologically based pharmacokinetic (PBPK) modeling approach.

Methods: A PBPK model for gold (Au) NPs in healthy mice was first developed based upon our previously
published model [2]. Then this healthy mouse model was extrapolated to include a tumor compartment to simulate the biodistribution of various inorganic and organic NMs (INMs and ONMs) in tumor-bearing mice. Multiple linear regression was employed to determine the potential effects of various physicochemical characteristics, including the hydrodynamic size, zeta potential, type of NPs, targeting strategies, cancer types, and tumor models on tumor delivery efficiency.

**Results:** The healthy mouse PBPK model well simulated concentrations of 13-nm AuNPs in plasma, lungs, liver, spleen, and kidneys in healthy mice after intravenous (IV) administration ($R^2 = 0.95$). The tumor-PBPK model also adequately simulated most of the tumor delivery efficiencies of 376 published datasets for multiple INMs and ONMs in tumor-bearing mice after IV injection for up to 168 h ($R^2 > 0.90$). Regression analysis indicated that factors including the size, surface charge, targeting strategies, cancer types, and tumor models had profound impacts on the tumor delivery efficiency of INMs; whereas NP-specific factors including core NMs, shape, size, surface charge, and cancer types significantly affected the tumor delivery efficiency of ONMs. The results also showed that the overall tumor delivery efficiency was estimated to be $\sim2.2\%$ ID (percentage of injected dose) based upon the published 376 datasets in the past 15 years using the tumor-bearing PBPK model. Subgroup analysis revealed that actively targeted INMs had a higher tumor delivery efficiency of $\sim4.7\%$ ID.

**Conclusions:** This PBPK modeling and simulation paradigm can identify main factors influencing NP tumor delivery efficiency. This approach may contribute to the design of new NP-based anticancer drugs with greater tumor targeting efficiency. (Supported by NIH NIBIB 1R03EB025566-01 and K-State CVM SUCCESS-FYI grants)


**T-070**

**Application of physiologically based pharmacokinetic (PBPK) modeling to predict fetal exposure to dolutegravir**

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**Objectives:** Physiologic changes associated with pregnancy have a large impact on drug disposition, which may lead to subtherapeutic or toxic exposures.1 The goal of this study was to build a maternal-fetal PBPK model to predict the fetal exposure to the HIV integrase inhibitor dolutegravir (DTG) at delivery.1

**Methods:** PBPK models were built in the Open Systems Pharmacology Software Suite version 7.3 (www.open-systems-pharmacology.org). The maternal-fetal PBPK model structure was developed in MoBi and exported to PK-Sim for population simulations. Placental transfer was parameterized based on information obtained from scaling equations available in the literature.1,2 The predictive performance of the PBPK models was evaluated via comparison with in vivo data collected from HIV-infected pregnant women receiving DTG as part of clinical care. Maternal plasma samples were collected at delivery, with the range of gestational age at delivery of 35 to 42 weeks, along with infant cord blood sample.

**Results:** For DTG, the estimated diffusion was $0.43 \text{ L/min}$ and the estimated placental partition coefficient was 0.4. A sensitivity analysis indicated that the fraction unbound is a critically important parameter for umbilical cord
concentration prediction. The parameters were applied to the DTG maternal-fetal PBPK model and the DTG concentrations in the umbilical cord were adequately predicted (see Figure 1). Seventeen out of 20 maternal samples fell within the 2-fold error range of the prediction, and 13/20 maternal samples fell within the 1.5-fold error of the prediction. Eighteen out 20 cord samples fell within the 2-fold error range of the prediction and 15/20 cord samples fell within the 1.5-fold error of prediction.

**Conclusions:** These results increase the confidence in applying PBPK models to predict maternal and fetal drug exposure. Data on protein binding of DTG in both the mother and fetus are needed to increase the confidence in the underlying induction of the main clearance pathway as well as to improve predictions of umbilical cord exposure. Improved maternal-fetal PBPK models may streamline and accelerate the performance of pharmacokinetic studies for drugs in pregnant women.

**References:**

**Figure 1:** DTG predicted maternal-fetal PK vs observed data. Blue line = cord blood geometric mean prediction; Blue shaded area = 5-95% percentile range; Blue circles = cord blood observed data; Green line = maternal geometric mean prediction; Green shaded area = 5-95% percentile range; Green circles = maternal observed data.

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**T-071**

**Physiologically based Quantitative Systems Pharmacology integrates Drug Development and Precision Medicine in Diabetes**

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**Objectives:** The complexity and heterogeneity of type 2 diabetes mellitus (T2DM) pathophysiology requires new approaches to drug development and personalized treatment to maximize their effectiveness and minimize cost. The development of new therapies requires a holistic understanding of the mechanisms governing the disease. We have developed a computational platform to enable drug development and design of optimal individualized medication strategies for new therapies for diabetes.
Methods: Both, the quantitative systems pharmacology (QSP) and the physiologically-based pharmacokinetics (PBPK) modeling approaches, are integrated within the computational PB-QSP Diabetes Platform. The platform was developed with the open-source Open Systems Pharmacology (OSP) Suite (PK-Sim® and MoBi®) (1) and is based on the previously published and open-source OSP Diabetes Platform (2, 3).

Results: The platform predicts glucose homeostasis in healthy and T2DM populations at organ and cellular levels (Figure 1). The model integrates the physiology and dynamics of glucose, insulin, c-peptide, glucagon, the incretin hormones GLP-1 and GIP (4), and HbA1C as a biomarker. Integrated drug therapies are intravenous (iv) and subcutaneous administrations of insulin (short- and long-acting), glucagon, and SGLT2(5) and DPP4 inhibitors. The model has been developed and qualified on published data from perturbation experiments including iv administrations of insulin, glucagon, GLP-1, and GIP, as well as iv, intraduodenal, and oral administration of glucose. The platform captures processes down to the tissue and cellular level, such as insulin receptor signaling in different target tissues.

Conclusions: The developed PB-QSP Diabetes Platform describes the regulation of glucose metabolism at a high level of detail with good accordance with the observed data. The integration of data across multiple scales allows to analyze novel drug targets and their treatment potential at different stages of T2DM progression. The PB backbone of the platform and integrated drug therapies allow leveraging the captured knowledge for clinical decision support strategies / precision medicine to identify the optimal treatment strategy for each patient.


Figure 1: Structure of the PB QSP Diabetes Platform. Schematic representation of the implemented processes. The Diabetes Platform incorporates PBPK models of glucose, insulin, c-peptide, glucagon, GLP-1, GIP, SGLT2 inhibitor dapagliflozin, and DPP4 inhibitor sitagliptin. Solid lines represent the most important processes in the relevant organs, dashed lines represent pharmacodynamic (PD) effects. GI: gastrointestinal, RBC: red blood cells,
GLUT4: Glucose transporter type 4, GLP-1: glucagon-like peptide-1, GIP: glucose-dependent insulinotropic polypeptide. Not all implemented processes and PD effects are shown.

T-072

Application of Quantitative Systems Pharmacology (QSP) model of COPD progression for evaluating a novel mechanism targeting oxidative stress and inflammation in the lung.

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Institutions: GSK, Collegeville, PA

Objectives: Chronic Obstructive Pulmonary Disorder (COPD) is primarily caused by long term (years) exposure to cigarette smoke. This complex disease progresses with coupled processes involving altered immune and tissue cell populations, inflammation, mucus production and tissue damage. A comprehensive platform QSP model describing COPD progression has been developed (1) and applied to predict the effects of a novel compound that targets oxidative stress and inflammation in the lung.

Methods: The compounds of interest enhance the cells’ ability to eliminate H2O2. Cytoplasm H2O2 is maintained at nanomolar levels in spite of millimolar extracellular concentrations (2, 3). Since H2O2 diffuses across cell membranes, the model accounts for these two very different environments. We incorporated intracellular reactions involved in ROS homeostasis in tissue and immune cells for the three lung compartments (upper airway, airway and alveolar), in addition to ROS production towards the interstitial space via NOX (Fig. 1a). The platform COPD model was further expanded to account for downstream protein accumulation and effects on COPD processes.

Results: The described model extensions allows for coupling drug PK to target engagement, effector protein levels, changes in cell populations, concentration of cell products, and tissue remodeling. The model is being actively used to translate in-vitro drug effects to COPD patients, understanding its effect on ROS homeostasis and inflammation. Model simulations are being used to: a) predict biomarkers time course at cellular, tissue and plasma levels (Fig. 1b); b) identify biomarkers with potential for significant changes in the short (hours) and long term (months); c) relate diverse drug regimens to outcome; d) identify patient populations most suitable for the therapy.

Conclusions: Extending the model to account for intracellular and extracellular environments allowed for a quantitative description of drug effect on ROS homeostasis and inflammation at cellular and tissue levels. Development of a platform QSP model allows rapid application to multiple COPD programs in GSK by adding drug specific effects in the platform.

Simplified scheme for ROS homeostasis, applied to macrophages, neutrophils, epithelial and endothelial cells in each lung compartment.

A. B.
Translational estrogen receptor (ER) modeling to predict a clinically efficacious dosing regimen for an oral selective estrogen receptor down regulator (SERD)

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1 Sanofi US: Cambridge, MA and Bridgewater, NJ  2 Sanofi France: Paris and Montpelier

Objective: The estrogen receptor (ERα) is a key proliferation signal in ER+/HER2- breast cancers, and modulation of ER activity is the fundamental mechanism of action for several classes of therapy. However, experiments suggest that ER levels are highly dynamic, and cellular levels can be replenished quickly. Modeling of ER dynamics can help optimize dosing regimens for endocrine-modulating therapies.

Methods: A semi-mechanistic model linking the pharmacokinetics of the oral SERD SAR439859, ER dynamics, and tumor growth was developed using in vitro assay and in vivo data from studies in tumor-bearing mice. The model allowed estimation of xenograft growth dependence on activated ER. By comparing the predicted efficacious mouse plasma concentration and human PK from a preliminary population PK model, a target plasma SAR439859 concentration and dosing regimen was suggested based on ER dynamics.

Results: The predicted critical levels of activated ER resulting in tumor stasis in mice are similar for both a wild-type and mutant ER xenograft tumor: 2.7 nM (90% CI 0.4 – 3.2 nM) and 3.1 nM (90% CI 1.1 – 4.2 nM) respectively. These concentrations are based on estimated steady state total ER levels of 49.8 nM in the wild type tumor and 149.5 nM in the mutant tumor, corresponding to 3x10^4 and 9x10^4 copies/cell, respectively. The plasma concentration of SAR439859 in mice predicted to maintain activated ER levels below this threshold is approximately 300 ng/mL in both cases. The human popPK model predicts that, on average, both a 400 mg QD and a 200 mg BID regimen will maintain plasma concentrations above this threshold.

Conclusions: Model predictions suggest a system with high sensitivity to activated ER levels. Moreover, the dynamics of ER replenishment show that an insufficient drug exposure for only a few hours per day could maintain tumor growth. Therefore, these factors support a dosing strategy that maintains maximal ER inactivation throughout the entire dosing interval and that, depending on drug PK properties, frequency of dosing could have efficacy implications. Future clinical evidence in human patients will confirm the recommended dose regimen and help to inform this hypothesis. Further, although FES-PET scans or biopsy analyses have shown significant ER engagement for SERD compounds, correlations between ER depletion and clinical outcomes have not been consistently demonstrated. Thus, models incorporating ER dynamics and tumor growth are very useful tools for assessing activity of SERDs and appropriate dosing regimens.


Application of a QSP model to dose selection for a BTK inhibitor in rheumatoid arthritis

Figure 1. A. Scheme for intracellular reactions involved in ROS homeostasis. B. Preliminary results with constant target engagement showing predicted change in biomarker levels in airway (aw) and plasma (pl) after beginning of therapy. Dotted lines: level in COPD patient prior to therapy. Dashed lines: level in healthy non-smoker.

Objectives: Selecting doses for a Phase II clinical trial in a disease population, such as rheumatoid arthritis (RA), where only Phase I target engagement data in healthy volunteers is available, remains challenging since there are no relevant clinical outputs (e.g. ACR score) from which to construct an empirical PK/PD model. Dose selection is particularly difficult when constrained by the number of doses that can be practically evaluated in a trial. We applied a QSP model for rheumatoid arthritis as a translational tool to bridge receptor occupancy with clinical efficacy for a covalent BTK inhibitor, LY3337641. The objective was to understand potential dose responses to help select a minimally effective dose for the Phase II trial.

Methods: A PK/PD model for receptor occupancy was constructed from single- and multiple-ascending dose Phase I data and incorporated into a QSP model. In vitro receptor occupancy assays were used as a bridge to estimate the equivalent in vitro concentrations of LY3337641 in PD assays that correspond to the clinical doses. Emax models were used to estimate inhibition levels for LY3337641 across three canonical BTK-related pathways in the model (B cell activation, FcR activation, and TLR activation) in addition to off-target effects. Virtual populations were constructed to fit Phase III clinical trial data from competitor molecules. Virtual populations were qualified by predicting the outcome for fostamatinib, a Syk inhibitor, which was not used for fitting. Potential dose responses were evaluated by fitting populations to maximize predicted efficacy of LY3337641 under different scenarios. The performance of LY3337641 was simulated across a dose range of 1 mg to 40 mg.

Results: The 1 mg and 5 mg QD dosing regimens resulted in 50% and 83% average receptor occupancy, respectively. Across all scenarios where LY3337641 was predicted to be effective, 1 mg was not predicted to separate from placebo. By contrast, simulations suggested that 5 mg could be a minimally effective dose.

Conclusions: QSP models can be used to provide objective mechanistic insight into Phase II dose selection when efficacy data are not available from Phase I studies. The QSP model helped to inform the low dose for the Phase II RA study dose range and allowed for a more efficient study design.

T-075

Development of quantitative systems pharmacology (QSP) model of systemic lupus erythematosus and its application to explore possible mechanisms of alterations in serum IFN1 resulting from anti-IFNAR1 treatment

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Objectives: To develop a QSP model of systemic lupus erythematosus (SLE) to explore in silico the effects of anti-IFNAR1 treatment on different patient subgroups.

Methods: The model was designed as a system of ordinary differential equations (227 reactions, 96 species) and parameters that were identified from literature data as well proteomic, transcriptomic and clinical data from the baseline population of the clinical study [1]. The model includes sub-modules describing:
- Life cycles of key cell types (dendritic cells, T-cells, B-cells and neutrophils) and their modulation by different factors
- Expression level of 21 genes (IFNGS) associated with a type I interferon (IFN1) dysregulation in SLE [2]
- Cytokine production by relevant cells and their dependence on endogenous and exogenous factors
- Cytokine distribution and clearance
• Pharmacokinetics and pharmacodynamics of the anti-IFNAR1 monoclonal antibody
• Complex clinical endpoint: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI2K)

**Results:** The model was validated using longitudinal data from the trial. The results show that the model adequately predicts:

- Suppression of the IFNGS during anti-IFNAR1 treatment
- Changes in blood cell counts and cytokine concentrations during anti-IFNAR1 treatment (example in Figure 1)

The model was applied to propose and explore possible mechanisms explaining the observed variability in the change (increase/decrease) of serum IFN1 concentrations resulting from anti-IFNAR1 treatment. The results showed that the direction of the change of IFN1 depends on the relative influence of the anti-IFNAR1 antibody on two oppositely directed processes: (i) production of IFN1 by dendritic cells; (ii) elimination of IFN1 due to receptor binding and subsequent internalization of the complex. The model predicts that patients with low values of IFNGS demonstrate increase in serum IFN1 but patients with high IFNGS can demonstrate either an increase or decrease in serum IFN1 depending on level of suppression of IFNGS upon treatment with the anti-IFNAR1 antibody.

**Conclusions:** The QSP model of SLE can be used to test a therapeutic hypothesis and for identifying patient subsets in the highly heterogeneous disease.

Objectives: Drug-drug interactions (DDI) are often modelled with rate laws for enzyme-catalysed reactions, which consider the impact of concomitantly administered perpetrator drugs. Thereby, the rate laws used are obtained by assumptions, which simplify otherwise more complicated equation systems. These assumptions are not fulfilled if, as in dabrafenib metabolism, enzymes either interfere with different sections of the same pathway or change in abundance. Nevertheless, inappropriate rate laws are often flexibilised to account for DDI or are accompanied by rather descriptive dose and time-dependent clearance terms to mimic CYP450 enzyme induction. Instead of using descriptive rate law adjustments, we strive for a quantitative system pharmacology (QSP) model based on a mechanistic ODE system for CYP3A to describe simultaneously all PK profiles related to both the cancer drug dabrafenib and concomitantly administered perpetrator drug ketoconazole.
**Methods:** We used the reaction network theory to construct the model and the genetic algorithm of Matlab’s global optimisation toolbox to estimate parameters. Sensitivity analysis was used to remove redundant model structures. The model structure is based on in vitro experiments, but the model parameters are estimated using clinical PK data exclusively (Ouellet, 2014; Bershas, 2013; Heel, 1982; Suttle, 2015).

**Results:** Our proposed network model reproduces dabrafenib metabolism and predicts an 8-fold maximum concentration of potent dabrafenib metabolites within four weeks in alignment with previously less heeded clinical ancillary results. Moreover, compounds sufficiently reduce the capacity of the enzymes and cause the DDI effect only because they utilize CYP450 enzymes for the biotransformation. We had neither to consider the pregnane X receptor to explain CYP3A4 transcription change nor rate laws for inhibitors to align with data. In addition, we argue that a self-regulatory mechanism of CYP3A4 is a suitable and more generalisable explanation for enzyme induction upon administration of xenobiotic drugs.

**Conclusions:** Our one-fits-all model can reproduce 19 different PK profiles of dabrafenib, ketoconazole, and dabrafenib-ketoconazole interaction under consideration of related dosage form and experimental context. Our work delivers a workflow helping others to use principles of QSP for regular PK questions.

**References:**


**T-077**

**Systems Pharmacology model characterizing the main immune components involved in Crohn’s Disease to test new therapeutic scenarios.**

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**Objectives:** Crohn’s disease (CD) is a complex inflammatory bowel disease causing a functional impairment of the gut wall. The reported lack of effectiveness in the standards of care together with the worldwide increase in CD incidence require the application of techniques aiming to find new targets and therapeutic strategies. At this point, systems pharmacology (SP) modelling gains importance as the available knowledge and modelling efforts (1,2) can be integrated into a single computational model. We aimed to develop a quantitative SP (QSP) model in humans characterizing the dynamics of the main immune components involved in CD.

**Methods:** We followed the six-stage workflow for robust application of SP modelling (3) to standardize the QSP model building. The turnover dynamics of the model components were characterized by zero- or first-order synthesis (ksyn) and first-order degradation (kdeg) rate constants. In cases where parameters were not directly available in literature, the corresponding estimates were obtained describing published raw data through non-linear regression in Rv3.5.0. Model selection was based on the akaike information criterion to select between different candidates. Ordinary differential equations-based models were implemented in SimBiology® (MATLAB®vR2018b). Once all the components were assembled, reported steady state levels in healthy subjects as
well as in CD patients were compared with the corresponding values obtained from deterministic simulations. Finally, a sensitivity analysis (SA) was performed to identify the most influential parameters.

**Results:** A total of 21 species representative of the innate and adaptive immune response in CD were included. Those species were (i) macrophages, dendritic cells and CD4+T cells, (ii) CD4+T cells subtypes (Th2, Th1, Th17 and Treg), (iii) pro-inflammatory ILs (IfNg, TNFa, IL12, IL23, IL6, IL1b, IL17, IL22, IL18, IL4, IL2 and IL15) and (iv) regulatory ILs (IL10 and TGFb1). In Figure 1 an overview of the model structure is provided, including the mathematical expression developed for one of the cells considered.

**Figure 1.** Graphical representation of the CD model and Th17 sub-model/ODE. An agreement between simulated and reported SS levels in both healthy subjects and CD patients was obtained supporting the structure of the final model. Results from SA show lack of major impact of any of model parameters on the SS levels indicating model robustness.

**Conclusions:** We present a QSP model for the main immune components in CD. This model proved to be promising for the *in-silico* evaluation of potential therapeutic targets and the search for specific biomarkers. Finally, it can be expanded or reduced as demanded, leading to different quantitative model/s to address research gaps regarding CD.

Linear and ensemble approaches for calibrating Quantitative Systems Pharmacology models more quickly and with reduced variability

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Objectives: Prior to applying a Quantitative Systems Pharmacology (QSP) model, a “virtual population” (VPop), representing alternative parameterizations of the model, is typically generated by calibrating the model to clinical data. Two challenges for virtual population calibration we wanted to address were (1) the speed of calibration algorithms that handle many virtual patients (VPs) and many clinical endpoint data, as well as (2) the ability of the algorithms to spread prevalence weights among many VPs [1,2]. We propose and characterize a method that linearizes a previously described VPop optimization problem formulation and instead solves a weighted non-negative least-squares regression problem. We also propose an ensemble algorithm which reduces the variance of the calibration and increases the spread of the prevalence weights.

Methods: We developed an alternative to our previously utilized prevalence weighting algorithm by linearizing the population statistical properties for endpoints and biomarkers of interest, here including means, standard deviations, bins, and distributions; and formulating the linearized calibration problem for weighted non-negative least-squares regression. Then, we use either the Lawson-Hanson or quadratic programming methods to optimize the prevalence weights. To ensure we had VPs that filled clinical distributions, we utilized VPs generated with a separately described iterative prevalence weighting and resampling method [3]. Next, we developed an ensemble algorithm inspired by the “feature bagging” algorithm commonly employed in machine learning applications. Specifically, the algorithm performs averaging across calibrations, each calibration being performed: (1) on a bootstrapped dataset, and (2) with a restricted subset of the VPs.

Results: The algorithm was substantially faster than a particle swarm method that solved the hypothesis test based objective function for optimization. In our evaluation case, a composite goodness of fit by Fisher’s method greater than 0.9 was achieved by both methods, but the solution for the linearized problem converged within seconds. The convex least-squares optimization problem contains a single basin of attraction provided the system is not underdetermined, and thus the prevalence weight solution doesn’t depend on an initial guess. However, two limitations of the algorithm are: (1) it doesn’t allow arbitrary objective functions, and (2) it didn’t result in good dispersion of prevalence weights among VPs (resulting in high variability of the calibration). The last consideration motivated the development of the feature bagging algorithm, which was very effective in dispersing the prevalence weights.

Conclusions: The method requires linearized representation of statistical properties for VPop calibration, but enables fast prevalence weight solutions that agreed very well with data. The method is currently incorporated into iterative VP resampling methods to speed the development of phenotypically representative cohorts of VPs in a high dimensional parameter space.

References:
A modeling workflow for quantitative systems pharmacology: Evaluation of MATLAB SimBiology vs. other MATLAB and R-based functionalities

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Objectives: Quantitative systems pharmacology (QSP), a mechanistically oriented form of drug and disease modeling, is increasingly impactful in model-informed drug discovery and development [1]. Consequently, a more standardized and seamless workflow for data structuring, model development, assessment, simulations and reporting is needed. In this work, we build upon a previously performed utility analysis of five different packages available for MATLAB and R [2], by evaluating functionalities of the MATLAB SimBiology toolbox within an existing modeling workflow framework.

Methods: We evaluated capabilities and performance of MATLAB SimBiology, by executing all steps of a designated modeling workflow framework, for three different QSP models with various mechanistic details and nonlinear features; we compared results against other toolboxes: the MATLAB-based IQM toolbox; R-based mrgsolve; RxODE; IQR.

Results: While all aforementioned tools were fit for QSP model development, with varying degrees of complexity and design, SimBiology’s unique emphasis on a graphical user interface provided the user with a choice of developing and evaluating a model via both scripts and a graphical interface. Similarly to IQM, IQR and mrgsolve, SimBiology worked with standardized ‘.csv’ datasets, although coded in wide (vs. long) formats. The overall solving speed of SimBiology was on par with other packages. The performance of the latest MATLAB SimBiology version 2019a has been enhanced vs. earlier versions (2013b), with 10-20% increase in solving speed and model compilation time, whereas the model code was fully translatable between various versions of MATLAB. While both IQM and IQR packages incorporated parameter estimation tools which were adequate for complex heterogeneous datasets with time-dependent regressors, only SimBiology offered a rich basket of at least 9 parameter estimation algorithms available for fixed-effects modeling and 2 for mixed-effects modeling, providing an opportunity to work with individual- and study-level data in one framework. SimBiology, IQM and IQR packages automatically provided common model diagnostics such as Observed vs. Predicted, Residuals and Time profiles plots. Similarly to IQR, SimBiology was able to estimate Gaussian, profile likelihood as well as bootstrap-derived confidence intervals for fitted parameters, thereby providing convenient tools for model identifiability analysis, together with a local sensitivity analysis capability.

Conclusions: SimBiology is a multi-feature modeling package with high emphasis on graphical interface and a full spectrum of model development capabilities, including use of standardized datasets, a rich basket of parameter estimation algorithms, integrated model diagnostics tools, as well as tools for model identifiability and sensitivity analyses.


Figure 1: QSP modeling workflow
Quantitative Systems Pharmacology Model of Acute Myeloid Leukemia: Prediction of Clinical Response Rates for Standard of Care Chemotherapies

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Objectives: Acute myeloid leukemia (AML) is a rapidly progressing hematological malignancy involving malignant blast cells in the bone marrow and blood. Chemotherapeutics such as azacitidine, decitabine and low dose cytarabine (ara-C) generally form the standard of care (SoC) in elderly patients with AML ‘unfit’ for intensive chemotherapy. There is an increasing number of targeted therapies in clinical trials that are being dosed in combination with the existing SoC drugs. The aims of this work were to develop an AML disease model, and calibrate the model to capture clinically observed dose-response relationships for SoC to provide a basis for efficacy predictions in combination clinical trials.

Methods: A systematic review of the literature was done to identify existing computational models for AML and unique features of these models were studied. A quantitative systems model was developed for AML disease progression based on the existing knowledge of hematological cellular lineages and progression. The model included myeloid progenitor cells in bone marrow and also terminally differentiated cells such as erythrocytes, platelets, monocytes, and neutrophils in systemic circulation. Clinical response data were identified for 36 cohorts spanning multiple clinical trials (~2000 AML patients) based on a comprehensive meta-analysis by Agarwal et al. (2017). External data from 5 additional cohorts were used to verify the predictive performance of the model.

Results: The model was able to describe homeostasis with respect to healthy cell counts in the bone marrow and blood in a healthy individual. After the introduction of malignant blasts, a significant reduction in circulating healthy cells was predicted in concordance with literature data. A linear dose-response for the SoC provided the best fit to the historical data. The linear dose-response was implemented within the AML model by capturing the drug effect by inhibiting the growth rate of blasts and healthy stem cells. After calibrating the drug effect, the AML model was verified to predict clinical responder rates (with < 30% prediction error) from 5 cohorts that were not included in the fitting dataset.
Conclusions: The developed systems model for AML was able to adequately capture the progression of the disease and dose response relations of SoC in AML patients reported in the literature. The model’s ability to show dynamic changes in blast counts and healthy cells can help inform the dosing regimens of both the targeted therapy and SoC to optimize therapy in combination clinical trials. Addition of mechanisms of relapse and resistance in AML to the systems model could provide further insights on therapeutic effects in various relevant patient populations.


Disclosure: Dwaipayan Mukherjee, Sumit Bhatnagar, Ahmed H. Salem, Rajeev M. Menon, and John P. Gibbs are AbbVie employees and may hold AbbVie stocks or options.

T-081

UNDERSTANDING CLINICAL OUTCOME OF ADUCANUMAB TRIALS IN ALZHEIMER USING A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL

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Objectives. Clinical trials with amyloid modulating interventions, such as Aducanumab (ADU) - an antibody with high affinity for aggregated forms of b-amyloid-in Alzheimer’s Disease (AD) have failed to show cognitive benefit despite substantial target engagement. We use a Quantitative Systems Pharmacology (QSP) model to understanding the biological basis of these clinical trial failures.

Methods. We implemented clinical data on amyloid synthesis, preclinical data on b-amyloid aggregation [1] and its effects on glutamate and nicotinic cholinergic neurotransmission (nACHR) [2] in a mechanism-based and ADAS-Cog calibrated QSP model of cortical microcircuits with 35 CNS targets [3]. Short b-amyloid peptides (a b1-40) are neurostimulatory over a limited dose-range, while longer amyloid peptides (a b1-42) have a monotonically increasing neuro-inhibitory effect. We showed previously that the cognitive readout worsens after BACE-inhibition, solanezumab and g-secretase inhibition at low baseline amyloid but improves at high baseline amyloid [4]. ADU’s effect is implemented using Michaelis-Menten kinetics of both oligomer and aggregate removal. We also simulated the pharmacodynamic effect of COMT, APOE and 5-HTTLPR genotypes and of donepezil, memantine and anti-depressants.

Results. We reproduced the observation that 10mpk of ADU after 52 weeks treatment (corresponding to more than 90% clearance of amyloid aggregates) is able to provide significant cognitive benefit in the range of 2-3 points on the ADAS-Cog scale [5] most likely in patients with high amyloid baseline, and with an AChE-I and an APOE4/4, COMTVal156Met/Met and 5HTT-LPR ss genotype. We then simulated at the virtual patient level the much larger ENGAGE and EMERGE aducanumab Phase III clinical trial at 40 months after enrollment (3055 patients) with the
recommended dose titration. We used the same distributions of common genotype variants and allowed comedinations in the smaller Ph1b trials and with random distribution of amyloid load above the threshold for positivity. The pharmacodynamic effect on amyloid oligomers was calculated from the observation that the highest dose eliminated all the amyloid plaques. Simulated group average outcomes did not differ significantly from placebo outcome at 110 weeks, as the variability was substantially greater than the effect size (ranging from 0.5-1 points worsening at low amyloid baseline to 1-1.5 points improvement at high amyloid baseline). Different scenarios of switching APOE4/4 subjects to lower doses – as happened during the trial, also lead to a lower efficacy. We also explored the effects of different distributions of the same patient population over the treatment arms.

**Discussion.** An advanced QSP model of cognition in AD can identify different hypotheses to explain clinical trial outcomes of β-amyloid modulation and illustrates the numerous non-linear pharmacodynamic interactions that affect clinical response. Application of this approach early on during clinical trial design can help mitigate negative PD-PD interactions and increase the probability of success.


**T-082**

**Towards an understanding of hERG potency variability derived from patch clamp protocols**

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**Objectives:** A multitude of different hERG potassium channel assays are available for early identification of cardiac repolarization risk. However, observed hERG IC₅₀s derived from different assays and even different voltage protocols within the same patch-clamp assay can be dramatically different, resulting in very different interpretations of the risk for QT prolongation. The goal of this work is to better assess and understand the protocol-dependent variability of hERG IC₅₀s.

**Methods:** A simulation-based approach allows voltage protocols mirroring various experimental patch-clamp and binding assays to be applied. A Markov model of drug binding to the hERG potassium channel [1] was used to
Results: Of the 28 compounds tested, only 17 showed complete inhibition of the hERG channel at the highest doses, reflecting that parameterization could be improved for the other 11 compounds. For the compounds that showed complete inhibition, simulations demonstrate that the patch clamp protocol used has a significant effect on the derived hERG IC$_{50}$. Certain protocols result in derived IC$_{50}$ values that are more potent than other protocols. However, the magnitude in the differences is not consistent across compounds. Across the 9 protocols, the differences range from 3 to 100-fold, indicating that the interplay between the binding kinetics of the compound and the kinetics of the channel opening and closing as dictated by the protocol ultimately determines the variability in the derived hERG IC$_{50}$.

Conclusions: In assessing the risk for QT prolongation, a molecule’s hERG potency value should be interpreted in the context of the assay/protocol used to obtain that value. This reinforces the need to have a standard hERG assay/protocol.


T-083

Applying Metropolis-Hastings sampling to QSP model to understand the variability in individual animal responses to anti-CTLA4 in CT26 syngeneic mouse model

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Objectives: Syngeneic mouse models have been widely employed in preclinical discovery of checkpoint inhibitors as they enable study of drug impact on the intact immune system. However, the interpretation of such studies remains challenging partly due to the large variability in individual animal responses to treatment. Previously we developed a Quantitative Systems Pharmacology (QSP) model for anti-CTLA4 in CT26 syngeneic mouse model. The model captures PK, tumor cell and intra-tumoral immune cell kinetics. In this work, we performed rigorous sampling approach to assess and quantify the parameter distributions for animals with different tumor growth inhibition (TGI) responses.

Methods: First, the parameters excluding PK and insensitive parameters were given a range 10-fold up and down from the nominal values in the previous model while the tumor growth and intrinsic death rates were bound by the estimates from the control group. Metropolis–Hastings (MH) algorithm was applied to sample the entire parameter space to obtain parameter samples admitted by TGI data for each animal. We then compared the parameter distributions for animals receiving the same dose with different responses, ie. good, partial and poor responders, and also compared animals receiving different doses with the similar responses. Next we kept the drug-related parameters such as biodistribution and binding affinity, the same for all the animals, used MH to sample rest of parameter space and compared parameter distributions to that from the first step.

Results: Despite all the parameters explored in MH sampling are sensitive parameters identified from univariate analysis, the marginal distributions for most of the parameters are fairly uniform except a few that describe tumor cell and T cell kinetics. Within the dose range tested (0.625 - 10 mg/kg Q3D with 3 doses), there are no substantial changes in the parameter marginal distributions whether drug-related parameters are kept the same for all the animals or not. For the responders from different dosing groups (0.625 vs. 10 mg/kg), there are no considerable changes in the parameter marginal distributions despite the difference in target occupancy on regulatory and effector T cells. Moreover, no single parameter is sufficient to explain the variability in TGI response, while the combination
of multiple parameters (e.g., tumor growth rate, CD8 proliferation rate and CTL killing rate) has the potential to predict different TGI responses.

**Conclusions:** A thorough exploration of the parameter space suggests multiple combinations of parameters can capture the TGI data variability. However, it also identified parameters constrained by the TGI data. It suggested that the TGI data alone are not sufficient to identify a single mechanism as the main contributor to the variability. The variability in TGI response is likely due to a combination of the biological variability related to tumor and immune cell kinetics.

**T-084**

*A population QSP model to capture individual tumor growth inhibition responses to anti-CTLA4 therapy in CT26 syngeneic mouse model*

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**Objectives:** Syngeneic mouse models have been widely employed in preclinical discovery of checkpoint inhibitors as they enable study of drug impact on the intact immune system. However, interpretation of such studies remains challenging partly due to the large variability in individual animal responses to drug treatment. Previously we developed a quantitative systems pharmacology (QSP) model for the checkpoint therapeutic antibody, anti-CTLA4, in the CT26 syngeneic mouse model. The model captures the PK, tumor cell and intra-tumoral immune cell kinetics. In this work, we applied nonlinear mixed effects (NLME) modeling approach to the QSP model to robustly capture variability in tumor growth inhibition (TGI) response.

**Methods:** The QSP model was developed previously in KroneckerBio, a modeling toolbox for Matlab. It was translated into Monolix to enable NLME modeling to capture individual animal TGI response. TGI data from two independent studies with the same anti-CTLA4 molecule and the same mouse model, but different tumor growth rates were available. The dataset from the study with more dose levels (control, 0.625, 1.25, 2.5, 5 and 10 mg/kg Q3D with 3 doses) was used as the training set. The dataset from the other study with only control and 10 mg/kg Q3D with 3 doses were used as the testing set.

**Results:** When interindividual variability (IIV) was added to the following parameters: tumor cell growth rate, 2nd order intrinsic tumor cell death rate, CD8 cell proliferation half-life, cytotoxic T cell half-life, 1st order clearance rate of damaged cells from tumor, the population model converged and adequately captured the individual TGI response from the training set. The parameters were selected because previous work showed they were among the top sensitive parameters and were also likely to be different among animals from Metropolis-Hastings sampling results. The estimated values for the 5 parameters are 0.282 /day (Q1 - Q3: 0.261 - 0.307), 3.45e+05 /day/nmol (Q1 - Q3: 3.29e+05 - 3.55e+05), 0.227 day (Q1 - Q3: 0.209 - 0.266), 5.39 day (Q1 - Q3: 4.05 - 7.49), and 0.0102 /day (Q1 - Q3: 0.00942 - 0.0107), respectively. For the testing set, the tumor growth rate was first estimated from the control group. The model was updated with the new tumor growth rate while fixing other parameters to the estimated values from the training set, and the predicted TGI responses with the model matched well the data in the treatment group from the testing set.

**Conclusions:** The population approach can be applied to a mechanistic model to capture the variability in TGI response. The result supports that the variability in TGI response can be explained by the biological variability related to tumor and immune cell kinetics. A population model like this is more interpretable, expandable and potentially translatable to human.
A quantitative systems pharmacology model simulating the effect of Tau antibodies on the inter-cellular spread of tau in Tauopathies

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Objective. Recent preclinical and human imaging studies using Tau PET tracers suggest that tau pathology follows well-defined neuro-anatomical trajectories in Alzheimer’s disease (AD) and related tauopathies. The use of Tau antibodies to prevent the formation and spreading of Tau aggregates is one of the leading strategies being tested clinically. To address the very low success rate observed in previous AD drug development efforts, we explore the utility of computer simulations of pathological progression using a spatio-temporal mechanism-based model. We believe this approach could help with clinical trial design optimization.

Method. A mechanism-based quantitative systems pharmacology (QSP) model of human biology and pathology integrates experimental preclinical in vitro and in vivo data relevant to mechanisms fundamental to the tau spreading hypothesis such as tau species diversity, neuronal firing activity-dependent Tau secretion, diffusion-limited Tau clearance, Tau binding to antibodies and HSPG receptors, uptake through pinocytosis and subsequent Tau internalization. Biological processes in the spatio-temporal slow axonal transport model include differential binding of free vs monomeric tau to microtubule, uptake of tau along the axonal membrane, templating of endogenous free tau with seed-competent tau and finally secretion of tau at a second synapse and uptake into a second afferent neuron (see model schematic below).

Results. The PK profile of 6 tau antibodies with 14-day injection cycles at 10 to 60 mpk (7 days half-life), a 0.1% brain penetration and affinities for monomeric and seed-competent tau is implemented together with a correction factor for the epitope site and phosphorylation status derived from experimental data. The time-dependent efficacy for reducing uptake of seed-competent tau after injection was calculated at six Braak stages using oligomeric tau levels derived from post-mortem human brains. The more selective antibodies (40E8 = CBDTau4.21 > Tau46>MC-1) were superior to DA31 and BIIB092 antibodies in their simulated prevention of Tau spreading. The efficacy of BIIB092 is dependent upon disease state, ranging from 20 to 55%, compared to CBDTau4.21 (range from 60 to 80%). The effect of comedications, genotypes and amyloid load resulted in an additional variability of 10-15% and is highly dependent upon the antibody and disease state. The effect of the antibodies is the greatest in early Braak stages and distal brain regions. The first appearance of seed-competent tau in a secondary neuron separated by a 600um axon, is detected after 14 days, a time in line with in vitro data. Sensitivity analysis of the model indicates that reducing the binding of seed-competent tau to anterograde motor proteins would lower pathology progression by 40%.

Discussion. The current version of this computational platform allows to simulate crucial pharmacodynamic interactions of tau antibodies in function of disease state, variations in neuronal firing due to comedications, genotypes and β-amyloid load. The long-term goal of this effort is to extrapolate this spatio-temporal model to the human situation using longitudinal tau PET tracer studies and neuroanatomical data. Quantitative estimations of these multiscale interactions are mandatory for designing successful clinical trials.
Benchmarking Optimization Methods for Parameter Estimation in Quantitative Systems Pharmacology Models

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Objectives: To assess the performance of different optimization methods for estimating parameter values for quantitative systems pharmacology (QSP) models of varying complexity and size.

Methods: In this work, we included a set of twelve optimization methods including scatter search, particle swarm optimization, simulated annealing, genetic algorithm, and multi-start method as discussed in previous research [1]. We evaluated the performance of each method for estimation of parameters in four different models: a standard target mediated drug disposition PKPD model and QSP models of PCSK9/LDL, Asthma, and T-cell dependent bispecific antibodies. These models represent a range of complexity, with associated numbers of unknown parameters ranging from 4 to 60. For each system, an objective function was created to compare the outputs of QSP models with experimental/clinical measurements or with simulated synthetic data with varying levels of noise introduced (0%-20%). Performance was evaluated based on the ability to find optimal solutions as well as computation time.

Results: We ranked the relative efficiency of different optimization methods by evaluating several metrics: 1) the ability to minimize objective value, 2) the number of objective calls needed to reach the optimal solution, 3) the trajectory of the objective value as a function of number of evaluations, and 4) a composite metric to calculate the percentage of time a given optimization method approaches a given vicinity of the optimal value across all the models and test scenarios. Heuristic methods such as particle-swarm optimization and scatter search, paired with a local optimization method, were found to generally be superior for the models considered; the multi-min method was found to be efficient for problems with large dimensions and some alternative methods were optimal for specific QSP problems (Fig. 1).

Conclusions: Among the optimization methods tested, particle swarm and scatter search methods [3] proved to be generally more efficient at estimating parameter values across a range of QSP models used. This work provides general guidance and information for selection of methods for parameter estimation based on the dimension of the QSP model and other considerations such as computational power and time.

Influence of neuronal protein degradation pathways on tau pathology studied by Quantitative Systems Pharmacology model

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Objectives: Alzheimer’s disease (AD) is characterized by progressive accumulation of Amyloid-β and tau protein aggregates and disruption of multiple cell processes: protein transport, degradation, and secretion. A quantitative description of interaction of these systems with protein accumulation may allow for better understanding of disease pathogenesis, risk factors, biomarkers and potential therapy mechanisms.

The objective was to develop a quantitative systems pharmacology (QSP) model describing the contribution of neuron homeostasis pathology or targeted treatment on tau accumulation, verified on data from a preclinical tau pathology model.

Methods: Tau pathology model [1] was merged with a new submodel for intraneuronal systems, interacting with tau pathological species: protein degradation via autophagic-lysosomal system (ALS) and cytoplasmic proteolytic systems, secretion (via exosome), sphingolipid and cholesterol metabolism. The model consists of ordinary differential equations for some key measurable biomarkers (e.g. ALS vesicle volumes, tau protein) and algebraic quasi-steady state equations for activating and inhibiting modulators (e.g. mTOR). Dysregulation of neuronal homeostasis during tau pathology in transgenic mouse was driven by interaction of tau protein with key regulators (e.g. proteasome inhibition) and disruption of transport system. The model was calibrated using public domain data on baseline concentrations in human brain and tau pathology in PS19 mouse. It was verified on multiple in vitro and preclinical data for interventions into cellular pathways.

Fig. 1. Performance of optimization methods as a function of number of evaluations needed to get to optimal point across different QSP models.
**Results:** The model correctly describes the baseline concentrations of cellular components in healthy human brain (77% simulations match data within 2-fold range, 80% of them are within 20% error). It also captures the accumulation of tau aggregates in transgenic mice (85% data within 2-fold range, 70% of them within 20% error) and tau seeding effect. Cellular in vitro responses to various compounds (e.g., rapamycin, vinblastine, ACAT, nSMase and proteasome inhibitors) are described correctly by the model, demonstrating that our model captures complex interactions between cellular pathways. Modelled contribution of ALS into clearance of tau aggregates was validated by comparing the simulated treatment effect of rapamycin to data in P301S mouse [2]. The model predicts a significant reduction in insoluble tau accumulation, comparable to the data (Figure 1), although there is a slight overprediction.

**Conclusions:** The model can be used as a mechanistic description of contributors to the accumulation of pathological protein species and has potential for making efficacy predictions for combinatorial treatments (e.g. tau targeted, and autophagy targeted). We expect that the developed model for the ALS system is going to be applicable to other toxic aggregates in different neurodegenerative diseases. For a more complete understanding of AD pathology in humans, a description for the interaction of amyloid pathology with the proposed system will need to be implemented.


Figure 1. Validation of the model: Comparison of model simulations for insoluble Tau fibrils with data for the reduction of insoluble Tau in the forebrain of P301S mice (measured by sarkosyl extraction) after treatment with Rapamycin between 3 to 4.5 months of age (left) and from 3 weeks to 5.5 months of age (right) compared to vehicle dosed [2]“
Using a mechanism-based stochastic model to predict tumor evolution and survival outcomes in patients with metastatic colorectal cancer: a retrospective analysis in 599 patients

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Background: Resistance is inevitable in almost all types of cancer treatments. Understanding tumor resistance from an evolutionary perspective can allow us to better predict the treatment outcomes and design evolution-proof therapies.

Objectives: The objectives were to use a stochastic tumor evolutionary model to analyze a phase III clinical trial data and to assess the evolutionary process of each patient and predict patient survival.

Methods: In this retrospective analysis, 599 patients with metastatic colorectal cancer were analyzed in total. The analysis was based on the changing liver lesion sizes over time. A stochastic model was constructed (figure 1A) to recapitulate the whole spectrum of tumor evolution from one malignant cell to a tumor bulk at diagnosis, then transient response to treatments till relapse. Degrees at which tumor cells proliferate, die, mutate to resistant cells, and respond to treatments were estimated for each patient using clinical data. A non-linear mixed effect (NLME) method was first applied to accommodate the sparse data for some patients. The stochastic model was then converted to its deterministic limits, to estimate individual parameters using stochastic approximation expectation-maximization (SAEM) algorithm in Monolix software. The stochastic model, with the ‘pattern search’ algorithm in Matlab, was applied to estimate parameters for each patient using the NLME-derived values as initials. At the end, a Cox regression model including patient evolutionary parameters and other clinical characteristics (selected by LASSO algorithm) was built to predict survival.
Results: Totally 599 patients with liver lesion size were analyzed, among which 137 patients were partial responders, and 290 were with stable disease. The evolutionary parameters were significantly different (p<0.01) across response status. Overall survivals could be adequately predicted by model-derived evolutionary parameters (figure 1B). The hazard ratios of these evolutionary parameters to overall survivals were: treatment killing effect [0.71 with 95% CI 0.62-0.81], cell death rate [0.82 with 95% CI 0.73-0.92], resistant cell growth rate [1.21 with 95% CI 1.08-1.35] and resistant sub-clone number (4 subtypes [1.33 with 95% CI 0.98-1.8] and ≥5 subtypes [2.23 with 95% CI 1.51-3.29]). The predicted numbers of resistant sub-clones at diagnosis were strongly correlated with treatment outcome and patient survival.

Conclusion: The stochastic model, using evolutionary theory, well described the tumor growth trajectory. In addition, the optimized evolutionary parameters adequately predicted survival outcomes in patients with metastatic colorectal cancers. (NIH R35 GM119661)
From stem cell to erythrocyte and platelet: QSP model of erythropoiesis and thrombopoiesis for assessing the impact of pharmacological interventions.

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Objectives: Cytokines-related emerging therapeutic strategies are very promising and affect the most sensitive physiological systems such as hematopoiesis. To predict the effect of pharmacological intervention on hematopoiesis-related clinical endpoints we propose the QSP model of erythropoiesis and thrombopoiesis.

Methods: Multi-compartment ODE model of erythropoiesis and thrombopoiesis was constructed to comprehensively describe cell dynamics from hematopoietic stem cell to circulating red cells and platelets. The model includes 20 state variables corresponding to specific stages of cell development distinguished based on morphology and surface markers expression. Model processes are cell self-renewal, differentiation, proliferation, migration from bone marrow into circulation and cell death. Binding of growth factors (SCF, EPO, TPO) and some interleukins (e.g. IL-3) to cell-surface receptors regulates cell dynamics with feedback on expression of the receptors. The model was calibrated across published in vitro/in vivo data including cell expansion under growth factors and cytokines exposure in vitro, flow cytometry cell counting of bone marrow aspirates and clinical data of erythropoiesis-stimulating agents’ administration. QSP approach combined with mechanistic PK/PD of growth factors and cytokines as well as biosimilars and drugs was used to describe cell proliferation and differentiation.

Results: Data-driven model satisfactorily describes clinical outcomes associated with erythropoiesis and thrombopoiesis, including baseline levels of various cell precursors in bone marrow and cell counts of red cells, reticulocytes, and platelets in circulation of healthy subject as well as corresponding alterations in hemoglobin/hematocrit levels. The response of clinical outcomes to administration of growth factors was also well described by the model. The model confirmed the main drivers of cell expansion are growth factors with different factors acting at specific stages of hematopoiesis, modulated by effector cytokines operating in synergy or as antagonists.

Conclusions: The proposed comprehensive human erythropoiesis and thrombopoiesis QSP model describes clinical data and could be seen as predictive tool for investigation of potential pharmacological interventions and explanation of observed phenomena. The model is regarded as a branch of developing a general platform of human hematopoiesis.

Virtual Patient Generation Strategies for Non-alcoholic Fatty Liver Disease

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Objectives: NAFLDsym, a Quantitative Systems Pharmacology model for NAFLD, integrates mechanisms that contribute to the key aspects of NAFLD disease pathophysiology, such as steatosis, lipotoxicity, inflammation and fibrosis. In this study we discuss our strategies to generate virtual patients for exploration of disease progression in NAFLD patients.

Methods: NAFLDsym v2A was developed by adding inflammation and fibrosis submodels to NAFLDsym v1A, which was described previously. Simulated patients were generated using two methods. In both methods selected mechanistic parameters were varied and simulations were run until the steady state was achieved. In the first method, the initial body weight was specified across a range, covering healthy and obese patients; caloric intake was set to maintain the specified body weight. The steady state conditions from these simulations included varied liver collagen content to represent patients at fibrosis stages F0-F4. In the second method, the simulated patients with initial body weight within healthy range and the steady state conditions from the simulations were used as initial conditions in the next round of simulations where increased caloric intake was applied over 20 years to stimulate weight gain and disease progression. Time points from these simulations were collected to generate virtual cohorts that represent F0-F4 patients and to analyze disease progression.

Results: The first method generates virtual patients under a stable diet and allows evaluation of the role of disease mechanisms on the propensity of an individual to develop fibrosis irrespective of change in diet and weight. On the
other hand, the second method tracks the weight gain and disease progression over time starting with healthy conditions, providing a physiologically relevant representation of the diet-induced NAFLD; however, this method comes with a cost in computational performance. In this study, the key features related to disease pathophysiology, such as disease progression rate and response to change in diet, were extracted from the plausible virtual patients generated by both methods; with plausibility being determined by comparing to non-interventional clinical studies. The exploration of the responsiveness of the virtual patients to dietary perturbations provided interesting insights about the possible patient phenotypes in NAFLD.

Conclusions: NAFLDSym and the presented strategies to generate virtual patients and cohorts for NAFLD expands the capabilities for the theoretical exploration of the impact of metabolic, inflammatory and fibrotic processes on disease progression for NAFLD patients.


T-091

Systems Pharmacology Modeling Identifies a Novel Treatment Strategy for Bortezomib-Induced Neuropathic Pain

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Objectives: To identify and experimentally evaluate a novel treatment strategy for the prevention of bortezomib-induced peripheral neuropathy.

Methods: A system pharmacology model of intracellular signaling and gene regulation in peripheral neurons was constructed using literature information and pathway databases. Network analyses were performed to identify potential drug targets that prevent bortezomib-induced neuronal apoptosis. The neuroprotective effects of a novel drug candidate, dexanabinol, were investigated using a microphysiological model of peripheral nerves and a rat model of bortezomib-induced peripheral neuropathy. The anti-cancer effects of the combination of bortezomib and dexanabinol were assessed in a mouse xenograft model of multiple myeloma. Drug effects on tumor growth kinetics were characterized with a computational drug interaction model.

Results: The system pharmacology model of neuronal signaling processes contained 131 nodes and 252 interactions. Attractor analysis identified that the combinatorial inhibition of TNFα, NMDA receptors, and reactive oxygen species (ROS) should prevent bortezomib-induced neuronal apoptosis. Dexanabinol was selected as a model compound for the treatment of bortezomib-induced peripheral neuropathy since the drug has been shown to inhibit all three of these targets. Bortezomib exposure (100 nM) in a peripheral nerve-on-a-chip device resulted in a significant decrease in proximal action potential amplitude (p<0.05) and distal nerve conduction velocity (p<0.001), which were partially restored by dexanabinol (10 μM). Bortezomib induced significant alterations in rat electrophysiological endpoints and behavioral studies of pain. Rats treated with dexanabinol and bortezomib showed a significant reduction in bortezomib-induced mechanical allodynia (p<0.01) and thermal hyperalgesia (p<0.01). No restorative effects were observed in nerve conduction studies. Dexanabinol did not compromise the anti-cancer effects of bortezomib, and computational modeling suggested that dexanabinol delayed tumor growth in mice in a synergistic manner with bortezomib (ψ=0.88).
Conclusions: A bottom-up network-based systems pharmacology approach identified potential drug targets and supported the hypothesis that dexanabinol may prevent bortezomib-induced peripheral neuropathy. Dexanabinol prevented the painful component of bortezomib-induced neurotoxic side effects in rats. Although electrophysiological endpoints were not met, dexanabinol might represent a clinically meaningful treatment of bortezomib-induced neuropathic pain and requires further investigation.

T-092

Development of a mechanistic representation of a stable solid tumor

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Objectives: One of the challenges in mechanistic modeling of a solid tumor in late-stage cancer is to accurately represent progressive tumor growth in untreated conditions and stable disease in response to immunotherapy. Published oncology models generally represent either complete resolution or tumor progression after treatment. Our goal was to create a virtual tumor which initially responds to treatment but then remains stable, and to identify key factors responsible for the stability.

Methods: We developed and qualified a mechanistic model representing a late-stage solid tumor, such as melanoma. The model includes a representation of tumor and immune cell life cycles (including cytotoxic, regulatory, and helper T cells, natural killer cells, and antigen presenting cells); recruitment, proliferation, and activation of immune cells; immune cell-mediated killing of tumor cells; various regulatory mediators; and a necrotic core. Different hypotheses and mechanisms to achieve tumor stability were implemented and tested. We evaluated response to immunotherapy by simulation of an anti-PD-1 therapy.

Results: Stable tumor volume post-treatment was achieved by including key biological mechanisms: 1) distinct tumor cell populations: one more susceptible, and one more resistant to T cell and NK cell cytotoxicity, with different levels of expression of PD-L1 and class I MHC; 2) a dynamic tumor volume, regulated by feedbacks from contact inhibition, immune cell recruitment and the necrotic core. An initial 60% decrease in tumor volume followed by stabilization for eight months under treatment was achieved by adding a stable population of MHC- tumor cells, which were necessary to maintain a population of MHC+ tumor cells susceptible to immune cell-mediated cytotoxicity. The inclusion of both tumor cell populations helped achieve a balance between tumor cell growth and anti-tumor response. A dynamic representation of the necrotic core was required to maintain limited tumor growth under therapeutic conditions. In addition, our in silico analysis showed that an overly complex representation of the mediator regulation of tumor and immune cell lifecycles led to redundancies that obscured instead of clarifying tumor behavior.

Conclusions: Mechanistic modeling identified critical factors that can lead to a stable response to immunotherapy, preventing tumor escape, but also preventing complete tumor regression. Introduction of two tumor cell populations and a dynamic tumor volume were key factors in achieving tumor stability. The model provides a framework for further research into understanding patients and tumor characteristics driving tumor escape versus stable disease or tumor regression under various treatments, and the development of more effective therapies to both exploit and overcome these mechanisms.

T-093

A qualitative and quantitative framework to assess the value of QSP modeling in pharmaceutical development.

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Objectives: While QSP modeling is becoming more prevalent, the question of how to assess the value of an investment in QSP modeling remains unanswered. QSP modeling uses data from the pathway to the outcome level to construct plausible hypotheses of biological systems. QSP models can be used to extrapolate beyond existing data to prospectively investigate novel questions, e.g., response to a novel target perturbation, identification of patient sub-types, the effects of protocol modifications, etc. Practitioners will readily attest that QSP models reduce uncertainty and provide learnings that inform future decision-making. But what are these modeling results actually worth? We lay out a framework for determining the economic value of QSP modeling.

Methods: We apply concepts from the professional discipline of Decision Analysis (DA) to illustrate the economic value of reducing uncertainty, in particular, about the biological hypotheses underlying proposed investments in pharmaceutical drugs, thus informing future program or portfolio decisions. We use a classic pedagogical problem from DA, the “Party Problem”, to illustrate key concepts and draw analogies to drug development decisions. The Party Problem involves a decision about where to hold a party, for example, indoors or outdoors, when there is a chance of rain. Despite its seeming simplicity, the Party Problem can be used to illustrate every conceptual and quantitative aspect of drug development decisions and provide guidance for assessing the value of modeling research.

Results: Like the Party Problem, pharmaceutical R&D decisions have all the features of typical decision problems. A decision is a choice between two or more alternatives (e.g., indoor or outdoor party/target A or target B). Each alternative has a different prospective value (e.g., an outdoor party is more fun/target A could be a blockbuster). The choice between the alternatives is complicated by uncertainty (e.g., will it rain?/will target A or target B be superior to standard of care?). If all uncertainty were eliminated, that is, with perfect information, the decision maker could easily choose the best alternative. QSP modeling reduces, but does not eliminate uncertainty – it provides helpful but imperfect information. DA provides a framework for putting an economic value on imperfect information by assessing the impact on predicted value and the ability to change one’s decision, taking risk sensitivity into account. In addition, concepts from DA illustrate the value of identifying new alternatives (e.g., party on the porch?/consider combining target A with an existing therapy?), identifying and resolving material uncertainties (e.g., chance of rain/the impact of target A on cell type X), and improved organizational clarity about the decision-making process, all of which are frequent benefits of QSP modeling in pharmaceutical development.

Conclusions: DA provides an attractive and holistic conceptual framework for valuing the contribution of QSP modeling to pharmaceutical development.

T-094

Workflow for development of QSP models of Immune Response requires appropriate software infrastructure

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Objectives: Development of QSP models describing immune response (IR) is associated with integration of different types of data used to establish the model structure (stoichiometry, regulatory feedbacks, rate equations), estimate parameters and validate predictive power of the model. Models of IR are characterized by following key features: modularity of structure, multiple cells/cytokines in several compartments/tissues, multi-effector regulation of cell dynamics processes, cell-to-cell interaction via secreted cytokines and surface molecules. Many questions arise during development of QSP models of IR, most of them are still open. For example, (i) how to describe combined regulatory effect of multiple cytokines and/or surface molecules on cell dynamics processes basing on in vitro and in vivo data; (ii) how to organize teamwork to reduce time and increase quality of model development? We aimed to suggest a workflow for development of QSP models of IR, propose answers to the questions formulated above and discuss software infrastructure suitable for development of QSP models of IR, their simulation and analysis.

Methods: QSP model of IR represents an ODE system with modular structure obtained by superposition of cell lifecycles. Cell lifecycle sub-model describes maturation, proliferation, migration, activation and apoptosis of
particular cell type, including regulation of these processes by multiple cytokines and surface molecules. Cell lifecycle sub-models are partially calibrated against *in vitro* data.

Software infrastructure includes:
- Three InSysBio databases: 1) Immune Response Template – IRT (lifecycles of immune cells); 2) *“in vitro* pars DB” (values of parameters estimated based on public *in vitro* data); 3) *“in vivo* baseline data DB” - CYTOCON (baseline concentrations of cytokines and cells)
- DBSolve software tool for model simulation and fitting
- qS3P programming framework for working with the large-scale QSP models
- Gitlab repository for teamwork and continuous development

**Results:** Proposed workflow (Fig. 1) starts with extraction of appropriate cell lifecycle sub-models from repository and their assembling to form “excel representation” of the model of particular disease associated with IR. This representation is converted to three other representations enabling proper model visualization, simulation and delivery. Two-step model calibration is implemented in the workflow: cell lifecycles are calibrated against *in vitro* data and then remaining unknown parameters are estimated via fitting of the final model against baseline *in vivo* data. Final model is predominantly validated against clinical trial data. Cell lifecycles are developed independently of assembling of the final model.

Based on the suggested workflow the models of IR in immuno-inflammatory diseases, hematological malignancies and solid tumors were developed (COPD, SLE, multiple myeloma and others).

**Conclusions:** Database dependent development of QSP models of IR was proposed. The workflow provides a way for development of the IR models and raises the question of availability of appropriate software infrastructure.

Fig. 1. Workflow for model development. Solid arrows represent stages of the workflow, dashed arrows indicate comparison of simulations produced by different software packages or simulations with data.
T-095

**A Quantitative Model-Based Framework to Optimize Clinical Outcomes in Neonatal Opioid Withdrawal Syndrome using Real World Data**

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**Background and Objectives**: Neonatal opioid withdrawal syndrome (NOWS) is a drug withdrawal syndrome that neonates exposed to opioids in utero may experience after birth. At least 75% of these neonates require pharmacotherapy for treatment, with morphine being most commonly used [1]. Currently, the morphine starting dose and dosing adjustments are often empiric or stepwise in nature with significant heterogeneity potentially leading to a longer hospital stay and increasing the economic burden. The aim of the study is to use a quantitative, model-based, real world data-driven approach to optimize morphine dosing in neonates with NOWS to improve clinical outcomes such as reducing time on treatment thereby reducing length of hospital stay.

**Methods**: Longitudinal morphine dose and clinical response (Modified Finnegan Score (MFS)) data along with maternal and infant baseline factors were collected using a retrospective cohort design from the electronic medical records of infants with NOWS (N=189, Observations≈100000) admitted to the University of Maryland Medical Center (UMMC)- Neonatal Intensive Care Unit (NICU) from 2013 to 2017. A dynamic linear mixed effects (DLME) [2] model which enables the current response to be regressed on the previous response, fixed effects, and random effects, was used to develop the relationship between MFS and morphine dose adjusting for baseline risk factors. An independent error covariance structure was assumed to be normally distributed. Model evaluation was performed using a simulation-based approach, utilizing the UMMC morphine dosing protocol, and comparing the observed and model predicted clinically meaningful metrics such as time on treatment.

**Results**: Prenatal methadone exposure, poly-substance drugs, the race of the neonate, previous MFS response and previous morphine dose were significant predictors of the current MFS response. Autocorrelations of previous two observed MFS with current observed MFS were $\rho_1=0.72$ and $\rho_2=0.25$ respectively, indicating positive correlations between consecutive MFS responses. On an average, for 100 micrograms increase in the morphine dose, the MFS decreased by 0.5 units. The model evaluation showed that observed time on treatment and model predicted time on treatment (median: 11.0 vs 9.8 days) was not significantly different (p = 0.28).

**Conclusion**: A model-based framework is developed to describe the MFS–morphine dose relationship using real world data. Further improvements to the DLME model is underway to develop an adaptive, individualized morphine dosing strategy for infants with NOWS that could lead to better clinical outcomes.


T-096

**New version of PFIM for optimal design in nonlinear mixed effects models using R S4**

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Objectives: Using the Fisher Information Matrix (FIM) to optimize the design of longitudinal studies is an efficient alternative to clinical trial simulation. PFIM 4.0 [1] is a R program devoted to the design evaluation and optimisation. Programmed in R S4 language, the new version of PFIM aims to increase the simplicity of use, the comprehensibility and the modularity of PFIM.

Methods: PFIM is re-programmed from scratch in RS4 language. The conception of the new PFIM is based on multiple classes and inheritances, with PFIM as a central object. The different programmed classes and objects are conceived to be easily used or modified for programmers and users of PFIM. The FIM is evaluated by first order linearisation of the model, as in PFIM 4.0. Under given design constraints and based on the D-criterion, the design is optimised using a multiplicative algorithm [2] which is a new feature as compared to PFIM 4.0. Several tests and examples on the new PFIM are used during the PFIM programming process. The results are compared to those obtained with PFIM 4.0.

Results: The new PFIM, by its conception, is different from PFIM 4.0. First, the use of the program is closer to most of R packages than PFIM 4.0. According to these different examples, the evaluated FIM is consistent with those obtained with PFIM 4.0. The different elements of a project can be stored as objects. Moreover, the project can be easily saved and reloaded. The design optimisation by the multiplicative algorithm allows one to optimize the number of arms, measuring times and doses at the same time. After a design evaluation and/or optimisation, the results can be presented in a summary, with the different elements that could be manipulated in R.

Conclusions: There is a need to increase the use of model based optimal design approaches, as it can anticipate ‘fatal’ studies. The new version of PFIM fulfill some needs by its usability. Nevertheless, this PFIM version is not final: some features implemented in PFIM 4.0. have to be also implemented in the new PFIM. The perspectives are also to implement new features such as alternative methods to evaluate the FIM for discrete response models. The results in this abstract have been previously presented in part at PAGE, Stockholm, 11-14th June, 2019 and published in the conference proceedings as abstract PAGE 28 (2019) Abstr 9003.


T-097

Bayesian individual dynamic predictions of biomarkers and risk of event in joint modelling (with uncertainty): a comparison between Stan, Monolix and NONMEM

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Objectives: Joint models of drug or biomarker kinetics and occurrence of event are increasingly used in drug development [1]. Given a joint model, Bayesian individual prediction of biomarkers and probability of event can be performed for new patients at different landmark times i.e. different time of collection of the individual data [2]. The aim of the present study was to compare the abilities of Stan, Monolix2018R2 and NONMEM7.4 to perform Bayesian individual dynamic predictions, with uncertainty, of biomarker kinetics and risk of death using simulated data.

Methods: Simulations of biomarker and survival data were performed using a mechanistic joint model of prostate specific antigen (PSA) kinetics and survival in metastatic prostate cancer. Several scenarios were evaluated, according to the strength of the association between PSA and survival (β): low link (β=0.05), high link (β=0.02) and a short survival scenario with a smaller Weibull scale parameter λ. For each scenario, one sample of N=200 patients using R software were simulated. Several landmark times s=0, 6, 12, 18 months were studied. For each individual
of each scenario, using individual data until each time s, a posteriori distribution of PSA kinetic individual parameters was estimated with each software. L=200 samples of individual parameters were drawn from the posterior distribution. For a horizon time \( t_h = T_{end} - (s+2) \) months, biomarker and survival predictions were computed. Relative estimation errors were used to assess bias and imprecision (RMSE) of individual parameter estimates. Similarly, bias and imprecision were also evaluated on individual PSA kinetic predictions at each horizon time. Moreover, coverages of 95% prediction interval of PSA and risk of death were also evaluated.

**Results:** We obtained similar results with each software tool. At each landmark, estimations of individual parameters had small biases regardless of the software. Imprecision on individual parameters was rather high but were similar with all software and showed marked improvements with increasing landmark time. In terms of coverage, results were roughly comparable with each software and this software were able to well predict individual PSA kinetics and survival during the follow-up. In terms of computing time, STAN using HMC algorithm was faster than MH software in Monolix and NONMEM to obtain individual parameters.

**Conclusions:** These findings suggest that Monolix2018R2, NONMEM7.4 and STAN are able to characterize individual dynamic predictions of biomarkers and risk of event in joint modelling framework with correct uncertainty and hence could be useful in the context of individualized medicine. The results in this abstract have been previously presented in part at PAGE, Stockholm, 11-14th June, 2019 and published in the conference proceedings as abstract PAGE 28 (2019) Abstr 9111.

**References:**

T-098

**vpcstats:** a new, flexible, powerful and efficient R package to compute VPC percentiles and prediction intervals

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**Objectives:** Visual Predictive Checks (VPCs) are widely used in pharmacometrics to validate models. When producing VPC plots, care must be given to stratification, censoring (concentrations below the limit of quantification) and binning, as these can dramatically impact the usefulness and interpretation of the result. While R-based tools for VPC generation are already available (vpc¹ package, PsN²/xpose³), current implementations lack flexibility, specifically with respect to binning (bins cannot be optimized differently across strata), LLOQ specification (it is assumed that the same LLOQ applies to all observations), and visual appearance of graphical output. This new R package overcomes these limitations by efficiently computing the VPC statistics, without imposing a graphical representation.

**Methods:** The vpcstats package makes computation of percentiles and prediction intervals fast and easy, while accounting for stratification, censoring, and binning. Basic plotting examples are provided, but plotting is kept separate from the main function to allow for more flexibility.

**Results:** vpcstats() takes as input a dataset of observations, a dataset of simulations, a stratification formula and a mapping of variables such as time, dv, lloq and nbins. It allows the LLOQ to vary for each sample. Another unique feature is that the user can specify a different number of bins for each stratum and choose to optimize the binning differently for each stratum. There are various ways to specify how the binning is performed: equal-sized, any method from the classInt⁴ package, or user-specified. In case of censored data, the user can choose to apply equal censoring to observed and simulated data. Pred-correction⁵ is supported. Any number of percentiles and prediction intervals around the percentiles can be specified. The data.table⁶ package is used internally to speed up computations.
The output of vpcstats() consists of data.frames that contain all the information about the observed and simulated prediction intervals for each percentile, as well as complete characterization of each bin. It can be plotted directly, or used to derive summary tables, as required.

Figure 1 highlights some of the distinctive capabilities of the package: by stratum LLOQ and binning. The number of observations in each bin is shown at the bottom of the plot, with ticks indicating the range of the observed data in each bin.

**Conclusions**: The vpcstats package is a flexible, powerful and efficient tool that helps the pharmacometrician to generate informative VPC output. The package will be available on CRAN, and is being developed at GitHub.

**Figure 1**: Example use of vpcstats.

References:
1. [https://cran.r-project.org/package=vpc](https://cran.r-project.org/package=vpc)
2. [https://uupharmacometrics.github.io/PsN/](https://uupharmacometrics.github.io/PsN/)
3. [https://cran.r-project.org/package=xpose](https://cran.r-project.org/package=xpose)
4. [https://cran.r-project.org/package=classInt](https://cran.r-project.org/package=classInt)
6. [https://cran.r-project.org/package=data.table](https://cran.r-project.org/package=data.table)

**T-099**

“Heta” is a New Declarative Language to Define the Large-Scale Systems Pharmacology and Systems Biology Models

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**Objectives**: Nowadays the mechanistic modeling in pharmacology and system biology moves towards the large-scale systems. The complex dynamic models with multiple levels and scales set new challenges: annotation of model components, visualization of structures and results, code management, simulation diagnostics and format transformations. The popular tools for modeling used different interfaces for development and editing models by
endpoint users: spreadsheets, visual-based, direct ODE writing, internal meta-language or mixture of them. Sharing the same model code within different tools is possible using standards as SBML[1], PharmML[2] and others but often the structure have limited capability on transformation simulation scenarios and datasets. Our study addresses two issues: the new format for storing QSP model structure, annotation, simulation tasks and experimental dataset as parts of entire format and human readable and writable text-based language for manipulating the modeling platform content.

**Methods:** Heta syntax is based on general purpose JSON format with some modifications to make the code human-readable, more expressive and modular. Heta-language parser was developed in NodeJS language. The language code editing is available in Atom editor which includes code checking and highlighting.

**Results:** Currently we present the first version (v0.1.0) of Heta-language. The components were organized in hierarchical classes: Species, Compartment, Model, Task, Dataset etc. Using the simple and intuitive syntax the users can create, modify model components and convert models to different formats. Ideologically Heta language has similarities with Antimony [3] but as we believe it is more flexible and intended for large scale QSP modeling. Heta-language has the following base properties:

- Modularity: QSP model can be subdivided to several modules for better project organization.
- Shared model parameters and datasets is helpful for the development of modeling platforms and parameter identification.
- Easy code parsing for potential implementation into different tools and frameworks.
- Reach annotation facilities for better code revision and reporting.
- Syntax flexibility for possible extension of implemented classes or creation new classes.
- Integration of Heta code with the external formats: sbml, dbsolve, excel spreadsheets.

Currently heta-structures support transformation to the following formats: mrgsolve, rxode, sbml, simbiology, dbsolve.

**Conclusions:** The Heta language can be used for the development of modular QSP modeling platforms integrating files of different formats and transforming to the unified data storage.

**References:**
Figure 1. Example of Heta code for one-compartment PK model in Atom editor.

T-100

Fast evaluation of experimental designs in non-linear mixed effects models with the PuMaS package

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Objectives: Compare the experimental design functionality in the new PuMaS package for the Julia programming language to the PopED package for Matlab.

Methods: A one-compartment model for warfarin with 32 subjects with a homoscedastic normal error model [1] was used for evaluating the two software packages for calculating Fisher Information Matrices (FIMs). The design was identical for all subjects and included a single dose event and eight observations per subject. For both packages, analytical solutions were used for evaluating the dynamic development of the drug concentration. Gradient calculations in the PuMaS package [2] were based on automatic differentiation (AD) while PopED [3,4] used a hybrid of complex step and finite differencing based numerical gradients.

Results: To evaluate the performance of the two packages, the determinant of the block Fisher Information Matrix (FIM) of the model was evaluated 1000 times in both packages. The timings include the evaluation of the FIM as well as the calculation of the determinant but exclude time for setting up the problem. Figure 1 indicates that PuMaS is ~25 times faster when evaluating the FIM compared to PopED in this example.

Conclusions: The new PuMaS package provides functionality for evaluating the optimal design in non-linear mixed effects models for pharmacometrics which is faster than Matlab version of the PopED package. Further investigations, including compilation time and evaluations of more complex differential equations models, are needed to show in which cases the PuMaS package is faster than other software tools. However, we conjecture that the performance of PuMaS will carry over to more complex models due to the AD approach taken by PuMaS together with Julia being a compiled language.

**T-101**

**QT/TdP Risk Screen: a web-based tool for the early identification and real-time assessment of drug-induced proarrhythmic and torsade de pointes safety risk**

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**Objectives:** While it is well recognized that early identification of drug-induced proarrhythmic safety risks is crucial to drug development for ethical, animal sparing and costs reduction considerations ¹, the availability of easily accessible, user-friendly tools for real-time assessments of the proarrhythmic potential of chemical compounds has been lacking. The novel Tx index², implemented in the new web-based QT/TdP Risk Screen tool, was applied to a dataset of 84 compounds.

**Methods:** The tool is based on 206,766 cellular simulations of compound-induced effects on Action Potential Duration (APD) in isolated endocardial, midmyocardial, and epicardial cells and on 7,072 tissue simulations on QT prolongation in a virtual tissue³. Simulations were performed by blocking the slow and the fast components of the delayed rectifier current (Ik and Ik, respectively) and the L-type calcium current (I_{CaL}) at different levels. Based on these simulations, the Tx index was defined as the ratio of drug concentration leading to a 10% prolongation of the APD or QT over the maximum effective free therapeutic plasma concentration. A dataset of 44 non-torsadogenic and 40 torsadogenic drug compounds was used to validate the performance of the tool. The tool is available on the InSilicoTrials.com cloud-based platform built on the Microsoft Azure cloud environment, in compliance with the highest standards of security and privacy.

**Results:** The classification of the 84 compounds resulted in an accuracy ranging between 87% and 88% for the four Tx index values (Tx_APD<sub>endo</sub>, Tx_APD<sub>mid</sub>, Tx_APD<sub>epi</sub> and Tx_QT). Receiver operating characteristic (ROC) curves were constructed on the four estimated Tx values for each compound in the dataset to enable the identification of torsadogenic potential cut-off values. These were identified as 8, 8, and 6.4 for Tx_APD<sub>endo</sub>, Tx_APD<sub>mid</sub>, Tx_APD<sub>epi</sub> and as 9.2 for Tx_QT, respectively. Each risk assessment required only a few seconds per compound.

**Conclusions:** The web-based, user-friendly QT/TdP Risk Screen tool enabled a highly accurate classification of 84 known drug compounds paving the way to a potential breakthrough in in silico proarrhythmic risk assessment.


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**T-102**

**Comparison of non-compartmental analysis results between PKNCA, PuMaS.NCA and Phoenix WinNonlin**

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**Objectives:** Noncompartmental analysis (NCA) is a primary analytical approach for pharmacokinetic studies, and its parameters act as decision criteria in many clinical studies including bioequivalence studies. This work was designed to compare the results of the R package PKNCA¹ and the Julia package PuMaS-NCA² with industry standard Phoenix WinNonlin³.
Methods: Approximately 100 datasets covering intravenous (bolus & infusions) and extravascular dosing, one-, two- and three-compartment drug disposition with linear, and non-linear clearance representing short and long half-life drugs, different absorption-lags, limits of quantification defined to derive 5 different levels of % area under the curve remaining to be explained by the data and 5 different levels of between-subject variability were evaluated. All these datasets were evaluated at single and multiple doses with a parent+metabolite model. The NCA analysis was conducted using the three software programs on the same computer to avoid differences.

Results: A numerical match of the results up to certain tolerances were obtained across the three software for all parameters of interest. Although the determination of the terminal rate constant uses regression testing in different software, the results for the terminal rate constant and the number of points used for its evaluation remained consistent and discrepancies did not impact the similarity of the main metrics of interest with respect to area under the curve, for example. Every effort was made to ensure that the settings for analysis were similar across the three platforms including using the same rule for handling missing and BLQ data. The simulation code used to generate the datasets and the datasets used for testing themselves will be available via an open GitHub repository.

Discussion: This work was undertaken to evaluate the interchangeability of the tools for NCA analysis. The results clearly show that the R based PKNCA, Julia based PuMaS-NCA and Phoenix WinNonlin can be used interchangeably to perform NCA analysis.


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Bioequivalence.jl: A suite of routines for bioequivalence (BE) analysis for the Julia language as part of the PuMaS ecosystem

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Objectives: Bioequivalence.jl is a Julia package that provides routines to perform bioequivalence analysis.

Methods: This contribution implements nine common study designs based on leading references in the literature such as Patterson and Jones (2006), Chow and Liu (2009), and regulatory guidance. The implementations are tested for accuracy against reference data sets such as Schütz, Labes, and Fuglsang (2014) and Fuglsang, Schütz, and Labes (2015). Additional tools are offered for special cases such as variability-scaled criterion for average bioequivalence (Haidar et al. 2008; Jiang et al. 2015). As part of the Julia pharmaceutical science ecosystem, it is integrated with the PuMaS.jl simulation engine for PKPD, PBPK, and QSP as well as the Non-Compartmental Analysis (NCA) module.

Results: The package can be used to analysis a series of bioequivalence study designs including: nonparameteric, parallel, two by two crossover, Balaam, dual, top two optimal two sequences four periods, and Williams designs for three and four formulations. In addition, it provides tools to analyze highly variable drugs (HVD) and Narrow Therapeutic Index Drugs (NTI) through a variability scaled framework. Relying on other tools in the Julia ecosystem, it allows additional functionality in designing and evaluating characteristics of bioequivalence studies.

Conclusions: Bioequivalence.jl is an open-source tool bioequivalence analysis in the Julia language. It is integrated with other projects to provide a comprehensive bioequivalence analysis pipeline. The project is active and supported
through a collaboration among the Center for Translation Medicine at the University of Maryland Baltimore, MIT, and Julia Computing.


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COMPLIMENTARY SHINY AND WIKI APPLICATIONS PROVIDE A DIGITAL WORKBENCH, ENABLING RAPID, RELIABLE, CROSS-STUDY, CROSS-INDICATION CONTEXTUALIZATION FOR ONGOING PROGRAMS

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OBJECTIVES: Scientists routinely draw context from literature and internal study data to inform program advancement decisions and trial design aspects (e.g. inclusion/exclusion criteria, stratification). To improve efficiency and meet ever-shortened timelines, a suite of complimentary user interfaces (UIs) were developed that enable rapid delivery of commonly requested clinical comparisons via broad access to trial information and accompanying data.

METHODS: Prior to building the suite of tools, types of common requests for landmark and longitudinal data comparisons were considered. The clinical study designs (parallel, crossover, re-randomized study arms) and forms of endpoints used (absolute values, change from baseline, % change, difference from placebo, etc.) informed the underlying database structure and tool functions needed to answer common study comparisons. Semantic MediaWiki (version 2.5.6) was used to surface information loaded from numerous Pfizer internal databases, Adis Insight, Thompson Reuters Cortellis and FDA’s trial registry at clinicaltrials.gov. Quality controlled subject-level databases were constructed by Pfizer Clinical Programming and Reporting group. UI graphics and analysis tools were developed using R (version 3.5 or later) and Shiny (version 1.2.0).

RESULTS: Five complimentary UIs were developed:
1. A Wikipedia-style web portal summary of >287,000 clinical trials from Pfizer and competitor sponsored trials, >48,000 drug profiles, links to >2,900 modeling and simulation reports, and 158 disease overview pages indexing all clinical studies (internal and external) and drugs, registered or in clinical development, for the portrayed diseases, descriptions of disease specific clinical endpoints, a catalog of internal pharmacometric analyses and reports performed in the disease area, and relevant external links including regulatory review documents. The wiki also contained documentation pages for the Shiny tools, including links to the profiles for the drugs, clinical trials, and clinical endpoints being used by each tool.
2. A disease-agnostic shiny application for accessing clinical labs and biomarkers database. The database contains data from 10 compounds evaluated within 78 protocols across 8 diseases, and the UI enable longitudinal summary
and subject level plotting, landmark comparisons with random effects calculations, and importing of literature or emerging data.

3. Three shiny disease-specific applications for Rheumatoid Arthritis, Ulcerative Colitis, and Crohn’s disease that focus on efficacy and disease specific biomarkers that allowing similar comparisons to the labs UI. These tools now reduce the time requirement for addressing many team questions regarding data availability and delivery of available comparisons from weeks to days or hours.

CONCLUSIONS: To surface trial information, reduce redundant practices of assembling custom datasets and constructing graphics, a complimentary set of UIs was constructed that:

• Delivers rapid and reproducible contextualization for trial readout interpretations
• Surfaces data and data sources for all scientist, facilitating data-into-knowledge transformation
• Enables simple, interactive exploratory graphical analysis allowing comparison across studies and competitor data for the patient population of interest.