

ASCPT 2017
ANNUAL MEETING

Quantitative Pharmacology Influence and Impact Initiative

Satyaprakash Nayak  & Sandra Visser 

Under leadership of ASCPT Quantitative Pharmacology Network leads:
Anne Heatherington & Karthik Venkatakrishnan

QP Influence and Impact Initiative

▼ Aim

- ▼ Develop slide repository with state-of-the-art quantitative pharmacology applications to increase awareness, advocacy for and education in the area of applied QP

▼ Alignment Goals of ASCPT 2015 Strategic Plan

▼ Influence and Impact:

- ▼ ASCPT is the scientific resource that influences decision-making on therapeutic usage for patient care

▼ Education and Communication:

- ▼ ASCPT builds upon its exceptional education offerings and family of journals to create value for members and new audiences

▼ Historical Perspective

- ▼ ASCPT task force advancing pharmacometrics and integration into drug development in 2010

- ▼ [iDecide](#) repository and [2010 CPT publication](#)

- ▼ Focus on creating repository of examples on regulatory decision making

- ▼ EFPIA Working group on Model-informed drug discovery and development (MID3)

- ▼ [MID3 White Paper](#) and [compilation of case examples](#)

- ▼ Focus on illustrating the MID3 framework (key questions on compound, mechanism and disease the various modelling approaches) along the drug discovery and development path all the way into the therapeutic use.

37 Case Studies on 5 Key Application Areas

▼ Translational medicine

- ▼ Novel methodology / framework
- ▼ Biomarker use
- ▼ Combination selection
- ▼ Clinical trial design optimization

▼ Drug development decision-making

- ▼ Dose/Schedule selection
- ▼ Outcome predictions
- ▼ Safety assessment

▼ Regulatory decision-making

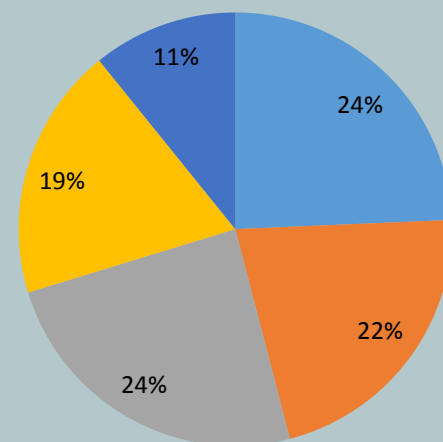
- ▼ Dose/Schedule Justification
- ▼ Label claims

▼ Therapeutic Use & Special Populations

- ▼ Pediatric dose setting
- ▼ Drug-Drug interactions
- ▼ Precision Medicine

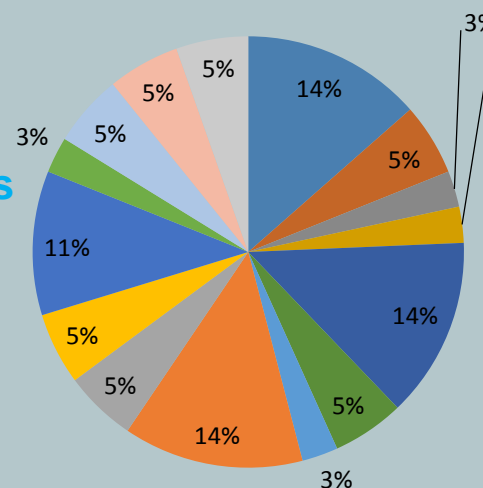
▼ Cost effectiveness & Differentiation

- ▼ Go/no go decisions
- ▼ Pharmacoeconomic assessment



Key Application Areas:

- Translational medicine
- Drug development decision-making
- Regulatory decision-making
- Therapeutic Use & Special Populations
- Cost effectiveness & Differentiation

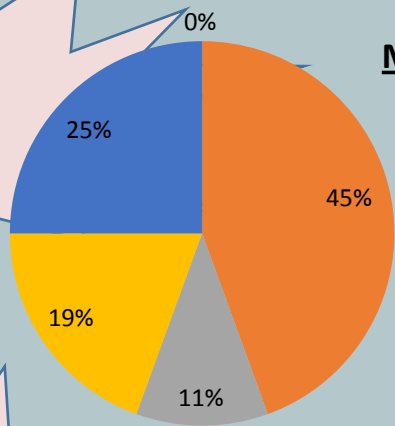


Key Application Sub-areas:

- Novel methodology / framework
- Clinical trial design optimization
- Biomarker use
- Combination selection
- Dose/Schedule selection
- Outcome predictions
- Safety assessment
- Dose/Schedule Justification
- Risk/Benefit evaluation
- Label claims
- Pediatric dose setting
- Drug-Drug interactions
- Precision Medicine

Emerging Trends observed in Case Studies

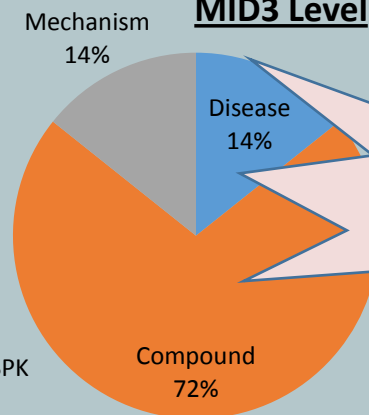
> 50% using novel QP approaches



Modeling Approach

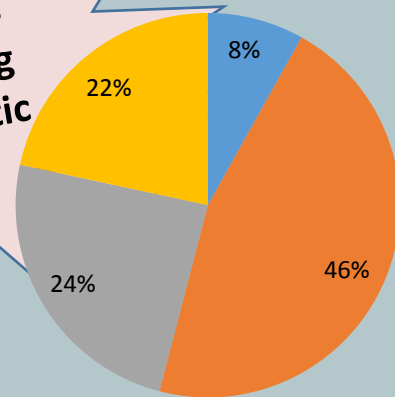
- Empirical DT
- Empirical PKPD
- MBMA
- Semi-mechanistic PKPD
- Systems Pharmacology and PBPK

MID3 Level



25% focusing on mechanism and disease

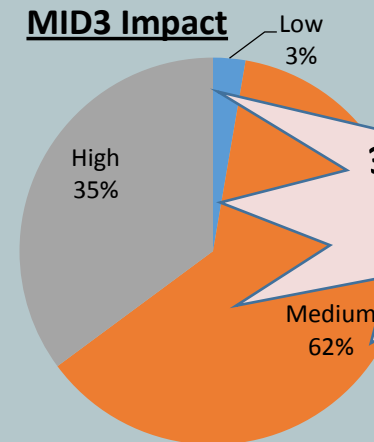
22% focus optimizing therapeutic Use



Development Phase

- Drug Discovery
- Drug Development
- Regulatory Interaction
- Therapeutic Use

MID3 Impact



35% "Replacing" experimental evidence

Continued Objectives for 2017-2018 QP Influence and Impact Initiative

- ▼ Publish Compendium at ASCPT Website
 - ▼ Link to compendium and speaker notes will be shared through ASCPT email burst
- ▼ Sharing Learnings in depth at ASCPT Webinar
 - ▼ Including 3-5 case studies
- ▼ Call for New Case Studies and Volunteers
 - ▼ Develop Version 2 of Compendium
- ▼ Develop leading Publication in ASCPT journal
 - ▼ Enhancing reputation of our QP community of practice

Acknowledgements

Feedback & Questions:

Satyaprakash Nayak & Sandra Visser



- ▼ QP network leads
 - ▼ Anne Heatherington & Karthik Venkatakrishnan
- ▼ ASCPT
 - ▼ Lisa Williamson
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Case Study Compendium

Table of Content

Translational medicine

Novel methodology / framework
 Biomarker use
 Combination selection
 Clinical trial design optimization

Drug development decision-making

Dose/Schedule selection
 Outcome predictions
 Safety assessment

Regulatory decision-making

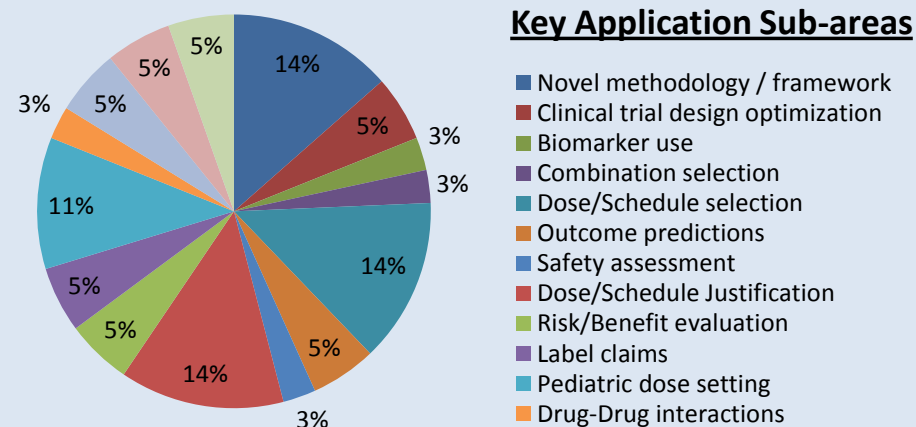
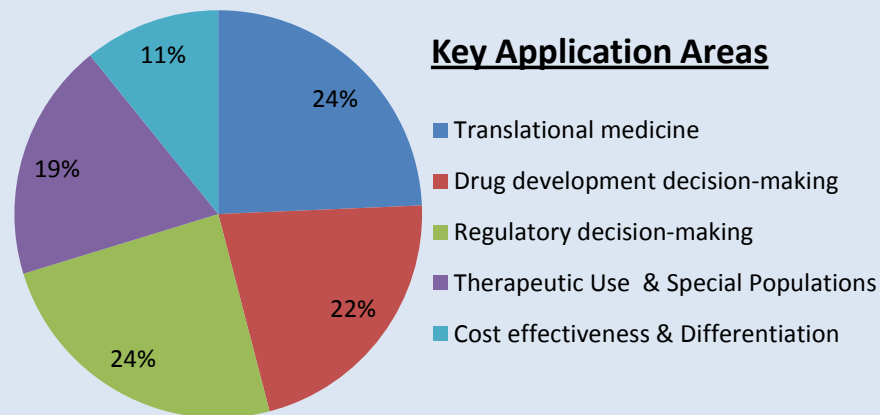
Dose/Schedule Justification
 Label claims

Therapeutic Use & Special Populations

Pediatric dose setting
 Drug-Drug interactions
 Precision Medicine

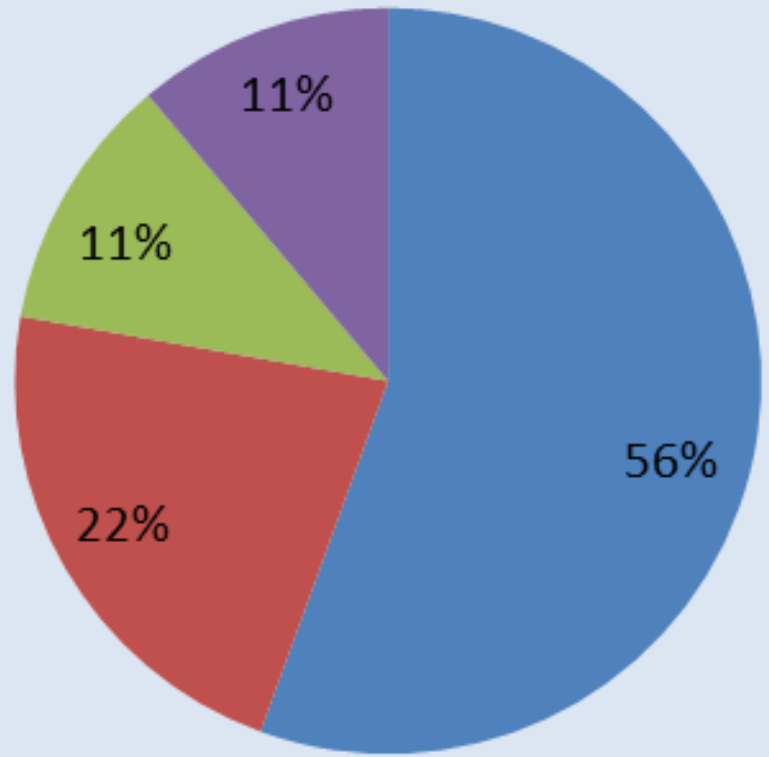
Cost effectiveness & Differentiation

Go/no go decisions
 Pharmaco-economic assessment



Key Application Area

Translational Medicine



Key Application Sub-areas

- Novel methodology / framework
- Clinical trial design optimization
- Biomarker use
- Combination selection

A framework for the quantification of QTc prolongation with a feasible ECG recording design in oncology patients

Key Question: How to assess cardiac safety in early oncology trials using optimal design and M&S approach?

- **Data:** PK and ECG in a phase I study in patients with cancer
- **Modeling / Analysis Method:** FIM-based optimal design for the computation of the expected power, then population PK/PD modelling
- **Results:** Concentration-QTc relationship, assessed taking into account individual dosing information, individual PK parameters, and circadian variations
- **Inference:** Analysis outcome ultimately will have to be compared to concentration range obtained at the recommended dose, in order to cover the variability of concentrations in clinical routine use

Study design

$N=100$
14 ECGs/individual
12 PK samples

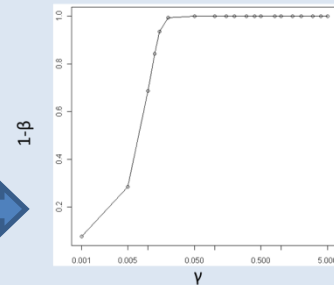
Putative PK/PD model:

$$QT_C(t) = QT_M(t) \cdot \left(1 + \sum_{n \in \{1,2,3\}} QTA_n \cdot \cos\left(\frac{t - T_{L_n}}{24/2^{n-1}}\right) \right)$$

$$QT_M(t) = QT_{M_0} \cdot (1 + \gamma \cdot C(t))$$

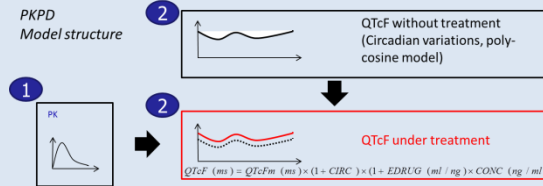
Optimal design

Power of detection of a drug effect as a function of drug effect value

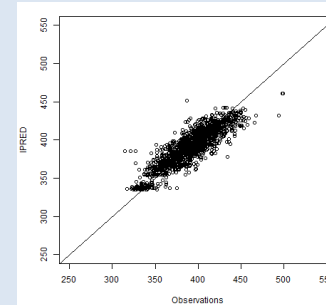


Study conduct

Population PK/PD modelling



PKPD model goodness of fit plot



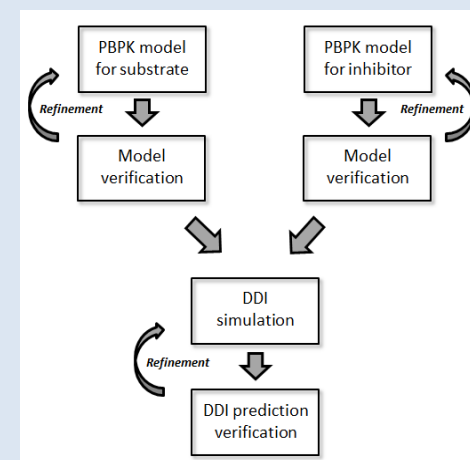
Conclusions: The combined use of optimal design before the study and population PK/PD analysis allows the assessment of the ability of the study design to inform on concentration-QTc relationship, and the quantitative assessment of this relationship



PBPK prediction of renal transporter-mediated DDI

Key Question: Can PBPK modelling (using in vitro inhibition constants) be used to predict renal transporter-mediated DDI?

- **Data:** PBPK model input parameters for a Servier drug (S 44121), ciprofloxacin, tenofovir and probenecid, and clinical DDI study results
- **Modeling Method:** PBPK models were created in Simcyp for S 44121, ciprofloxacin, tenofovir and probenecid. Simulations were carried out, and predictions were compared to observed data (i.e. concentrations from clinical DDI study).
- **Results:** The PBPK model slightly underpredicted the extent of interaction between S 44121 and probenecid when using the in vitro K_i value. The model correctly predicted that there would be no interaction between S 44121 and tenofovir or ciprofloxacin.
- **Inference /Simulation / Extrapolation:** The simulation showing that no DDI was expected between S 44121 and tenofovir or ciprofloxacin means that a clinical DDI study might have been avoided, if accepted by the regulatory agency.



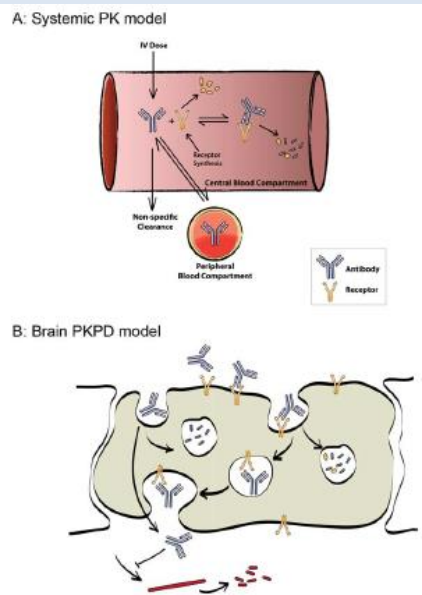
Conclusions: Overall, the PBPK modelling approach gave a better prediction of the extent of DDI than the static predictions based on inhibitor C_{max} and IC_{50} , therefore this can be considered a potentially valuable tool within drug development. More examples of this type are nevertheless required before it can be used to potentially replace clinical studies.



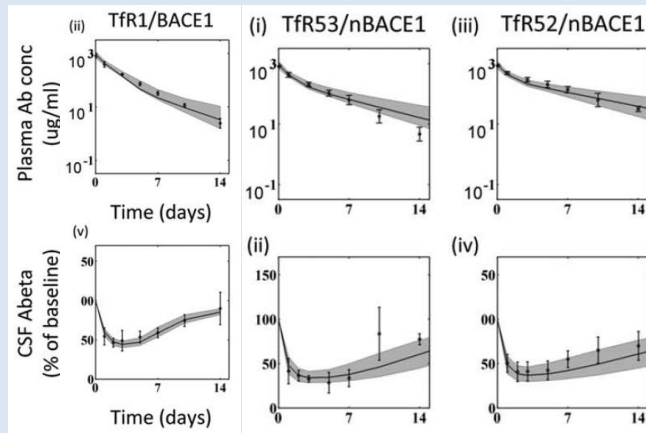
Prospective Design of Anti-Transferrin Receptor Bispecific Antibodies for Optimal Delivery into the Human Brain

Key Question: How can we predict optimal anti-TfR affinity for human brain penetration and expected clinical activity of anti-TfR bispecific antibodies based on preclinical studies?

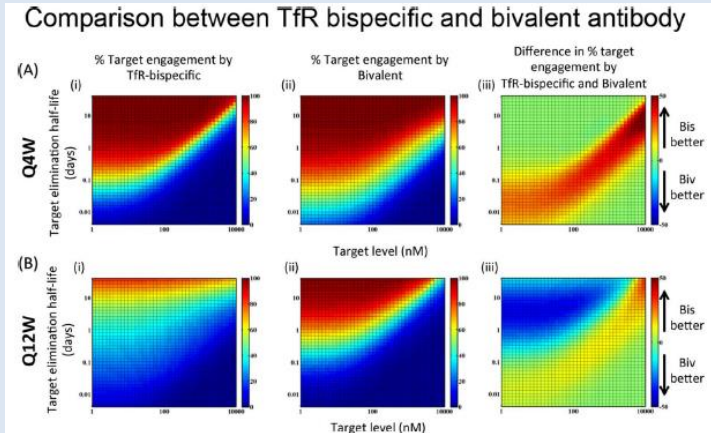
Model Structure



Model calibration/validation



Differentiation Potential



Inference: The proposed modeling framework is capable of predicting antibody PK and CSF PD for a wide range of brain-targeted antibody characteristics in nonhuman primates. The workflow allows predictions for expected human response to anti-TfR bispecifics targeting brain-targets at varied concentrations and turnover rates.

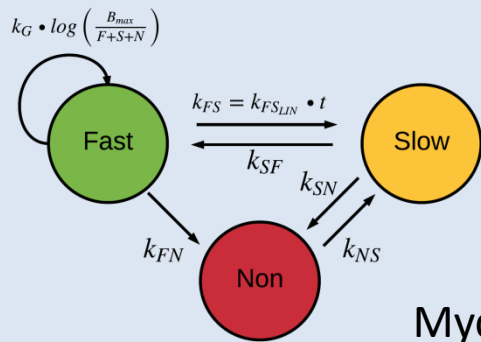
Conclusions: The described modeling and simulation framework could predict the profile of expected human target neutralization for a specific antibody against a specific brain target. Thus, this modeling and simulation framework can play a prospectively instrumental role in specifying criteria for designing optimal clinical candidates and efficient clinical studies to enable faster development of this class of therapeutic bispecific antibodies.



Preclinical to clinical forecasting in tuberculosis drug development using a translational pharmacometric approach

Key Question: How to optimally select clinical anti-tuberculosis drug combination regimens from preclinical studies using a translational pharmacometric approach?

Pre-clinical Disease Model

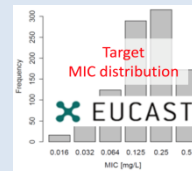


Translational Factors

Target site exposure



Mycobacterial factors

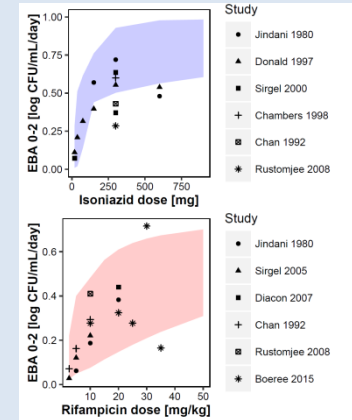


MIC distribution



PK covariates

Clinical Predictions



Inference

- Closing the translational gap between preclinical and clinical development in TB drug development.

Conclusions

- The presented translational pharmacometric approach predicted the (joint) dose response for common TB drugs from pre-clinical exposure-response studies
- This allows forecasting of (combined) exposure response in TB to inform innovative phase IIa/b regimens and designs, in which drug effects cannot be studied in monotherapy



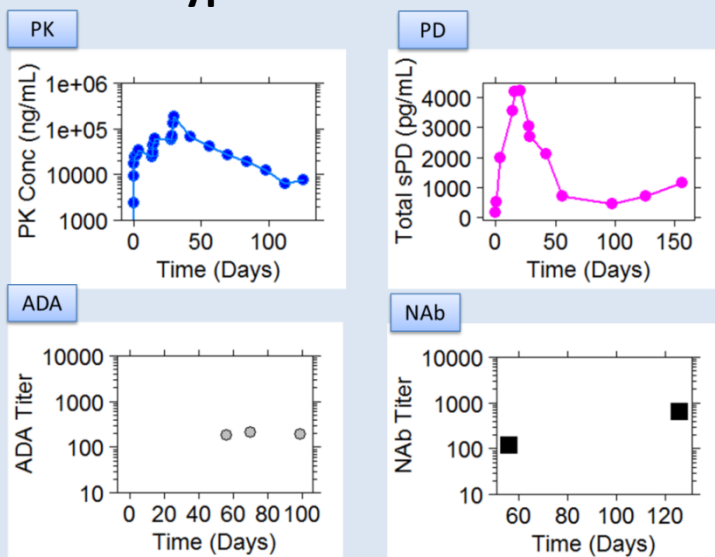
Enhance Visualization of Biologic PK, PD, ADA & NAb Data

Key Question: Is there an integrated way to visualize biologics PK, PD, ADA & NAb data?

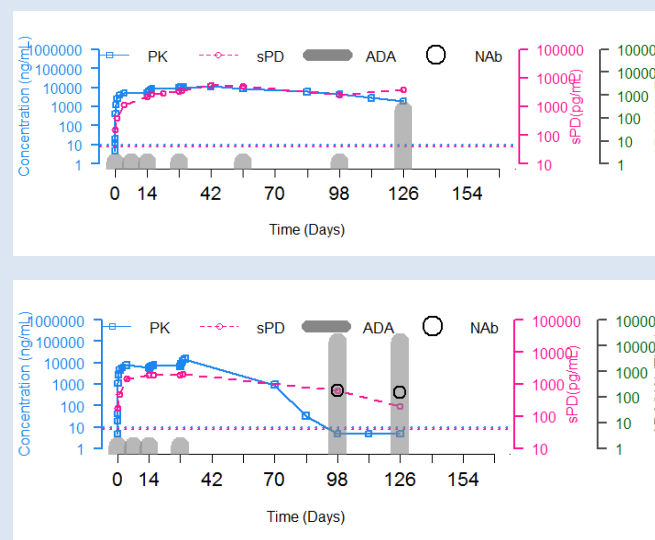
Background: Typically PK, PD, ADA and NAb data are summarized/plotted into different figures and often the interpretability is lost as one has to toggle through different plots

Method: An integrated visualization using R along with RShiny makes the data integration easier for decision making.

Typical Visualization



Integrated Visualization



Conclusions: Integrated visualization enabled efficient decision regarding the impact of ADA & NAb data on PD and PK of a biologic molecule. This improved and informed project decision making time



A higher scopolamine dose is required to obtain a more robust and consistent effect size in scopolamine challenge studies

Key Question: Can a meta-analysis help to optimize scopolamine challenge study design to evaluate NCEs targeting cognition impairment?

Data

- Clinical studies: five Phase I, placebo controlled studies were pooled for the analysis of PK and PD data. 159 healthy volunteers receiving 0.5 or 0.8 mg scopolamine alone or with 10 mg donepezil
- PD endpoints: Detection time (DET) and Groton Maze Learning (GML)
- Large variability was observed in the response with different strength in signal across the available PD endpoints (Figure 1)

Modeling

- Both scopolamine and donepezil PK were described by a two-compartmental model with first order absorption and lag time
- An indirect effect model with effect compartment accounting for the dissociation between PK and PD measurements described the PKPD relationship
- Scopolamine effect was assumed to be proportional to baseline; similarly donepezil effect was assumed to be proportional to scopolamine

Results/Simulations

- DET and GML time-courses were well described by the models developed (Figure 2)
- Median [95% CI] donepezil effect in attenuating the scopolamine-induced cognition impairment was estimated to be 27.4% [26.1-28.8] for DET and 42.9% [34.5-50.6] for GML
- Simulations show that 0.8 mg scopolamine, as compared to the commonly used 0.5 mg scopolamine, provides a 2-fold increase in the population signal with a direct benefit on the relative PD response (Figure 3)

Figure 1: Time course of DET (left), GML (right). Placebo data are presented in yellow. Scopolamine data are presented in black (0.5 mg) and blue (0.8 mg). Solid lines represent median profiles.

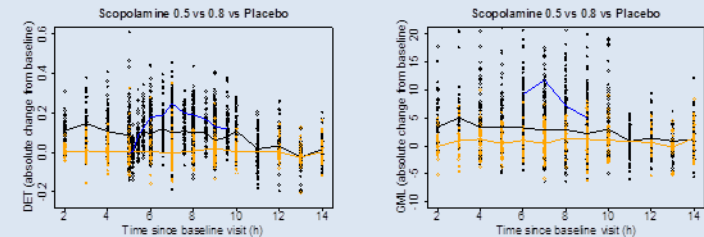


Figure 2: Median observed and predicted profiles of DET (left), GML (right). Solid lines represent treatment arms receiving scopolamine only whereas dashed lines represent scopolamine + donepezil arms. Black and grey lines represent respectively observed and predicted data in individuals receiving 0.5 mg scopolamine whereas blue and red lines represent respectively observed and predicted data in individuals receiving 0.8 mg scopolamine.

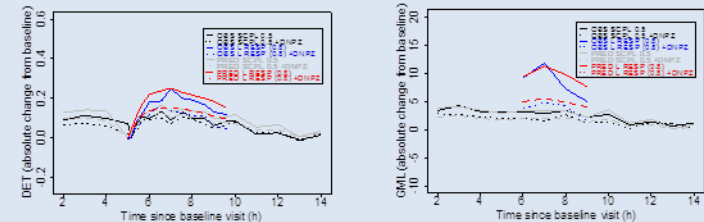
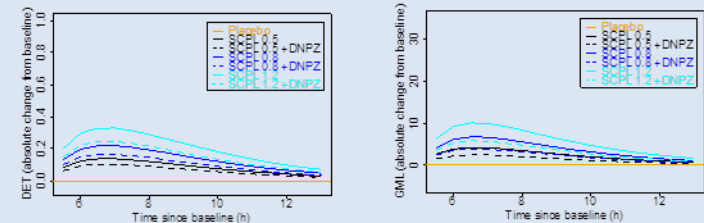


Figure 3: DET (left) and GML (right) simulated median profiles. Solid and dashed lines represent respectively scopolamine and scopolamine + donepezil treatment arms. Yellow = placebo; black/blue/light blue = 0.5/0.8/1.2 mg scopolamine



Conclusions: PKPD relationships of DET and GML were successfully characterized providing a framework that allows optimization of scopolamine challenge studies



Design and comparator insulin dose setting for multi-glycemic clamp studies of novel insulin mechanisms

Key Question: How does the insulin PKPD relationship change as a function of glucose clamp target in clinical studies to enable design of multi-glycemic clamp study and dose selection for comparator arm?

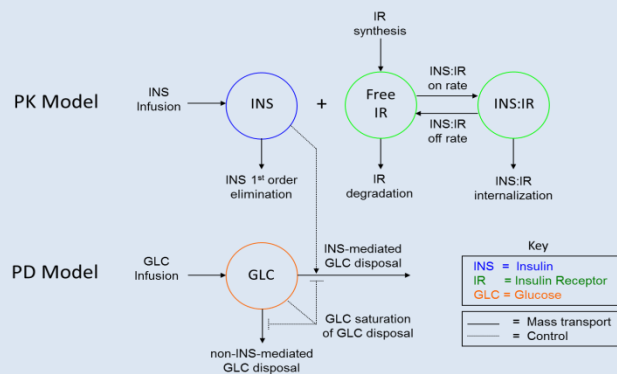
Data: Literature clinical studies

Methods: Translation between HV and T1DM patients, and between glycemic levels done by building a clinical comparator model for regular human insulin PKPD data in clamp studies.

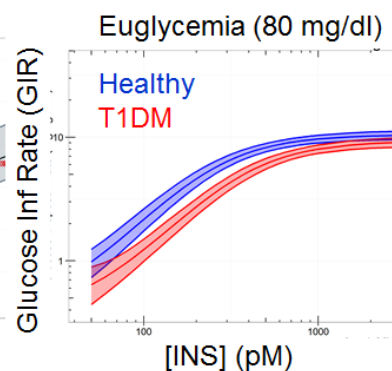
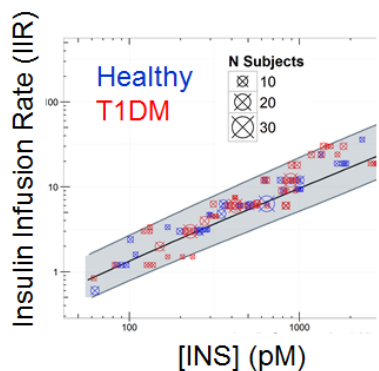
Results: Insulin CL saturable without PK differences HV/T1DM
Insulin action is function of glycemic target. Insulin is less potent in T1DM compared to HV combined with reduced maximum.

Population	Sources (Obs)		Data range (GLC -mg/dl, IIR -pmol/kg/min)			
	PK	PKPD	GLC ≤100	GLC >100	IIR ≤10	IIR >10
ND	15 (58)	14 (53)	37	21	36	22
T1DM	17 (71)	15 (56)	45	26	44	27

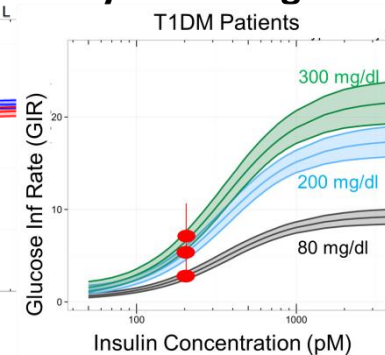
Clamp PKPD Model: Diagram



Translating from **HV** to **T1DM**



Projecting PKPD at
Glycemic targets



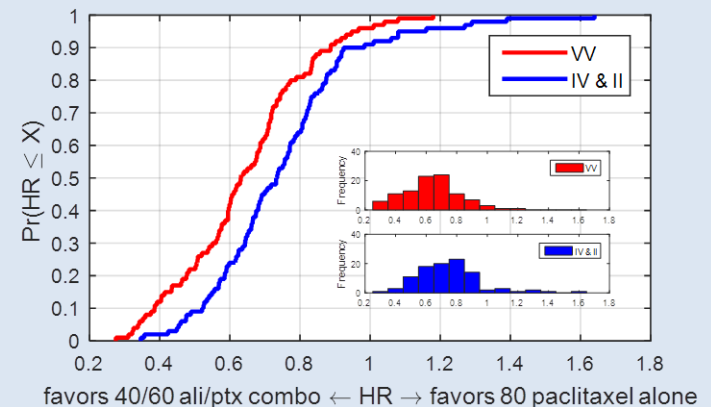
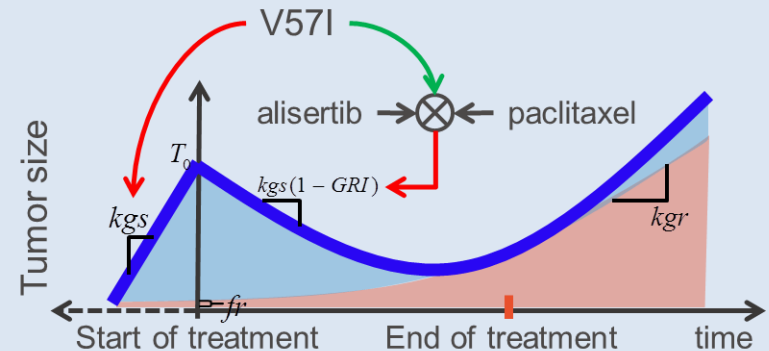
Conclusions: A joint PKPD mechanistic model can describe and explain insulin PK and action during the hyperinsulinemic clamp for T1DM and ND populations and varying glycemic levels. This model was used to design the comparator arm for (multi) glycemic clamp studies in both healthy subjects and T1DM patients.



Dose-exposure-tumor kinetic modeling to determine strength of baseline biomarker as driver of antitumor effect

Key Question: What are the (baseline biomarker) drivers of antitumor effect, once dosing and exposure variability are accounted for?

- **Data** from 107 ovarian cancer patients
 - Dosing records (alisertib & paclitaxel)
 - AAK SNP status
 - tumor size (TS) assessments,
 - individual popPK parameters
- **Modeling Method**
 - Nonlinear mixed effects dose-exposure-antitumor effect
 - Test AAK SNP status as covariate
- **Results**
 - SNP status of AAK (target of alisertib): significant covariate
- **Simulations**
 - Simulations predict VV genotype is 10-20% more likely to show a progression-free survival advantage of alisertib/paclitaxel combination over paclitaxel alone.



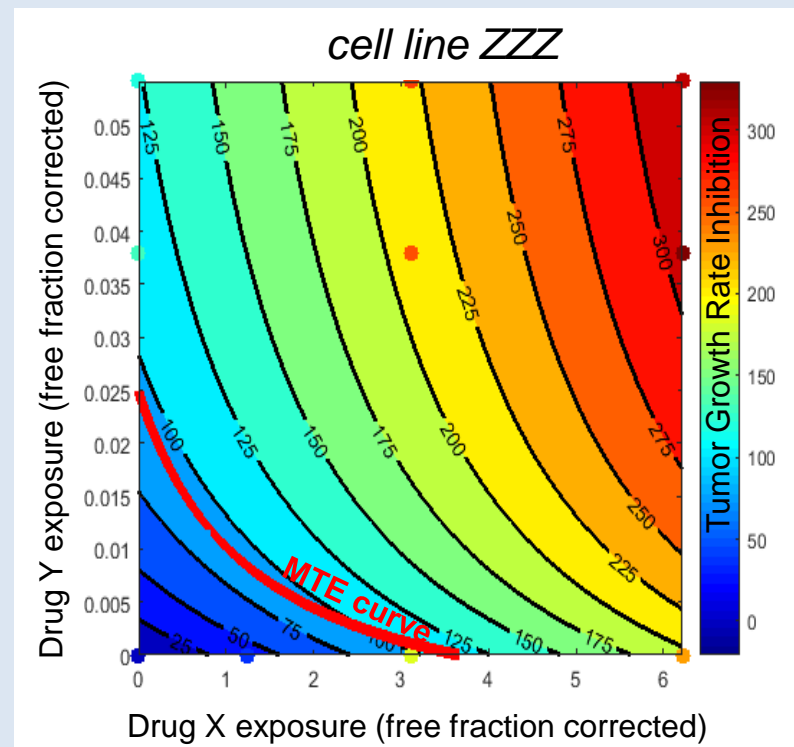
Conclusions: Tumor kinetic modeling considering dosing and PK variability with baseline biomarkers as covariates can provide more precise estimates of biomarker contribution to observed variability in antitumor drug effects.



Simultaneous safety/efficacy modeling to determine optimal doses for an anticancer drug combination

Key Question: Given observed clinical toxicity and our preclinical understanding of exposure-response, what tolerable dose pair will give optimal antitumor effect?

- **Data:**
 - Combination (+ mono if available) exposure & toxicity data.
 - Preclinical exposure & tumor growth data.
 - Protein binding in mouse & man.
- **Modeling / Analysis Method**
 - 2D logistic regression on free fraction exposure/tox data → **maximum tolerated exposure (MTE) curve**
 - Surface fit to preclinical free fraction exposure/effect data.
 - Calculate effect along MTE curve → optimal exposure ratio
 - Convert exposure back to dose
- **Results:** in tested (blinded) combo, toxicity was more synergistic than efficacy
- **Inference:** optimal dose = drug X given as monotherapy at MTD

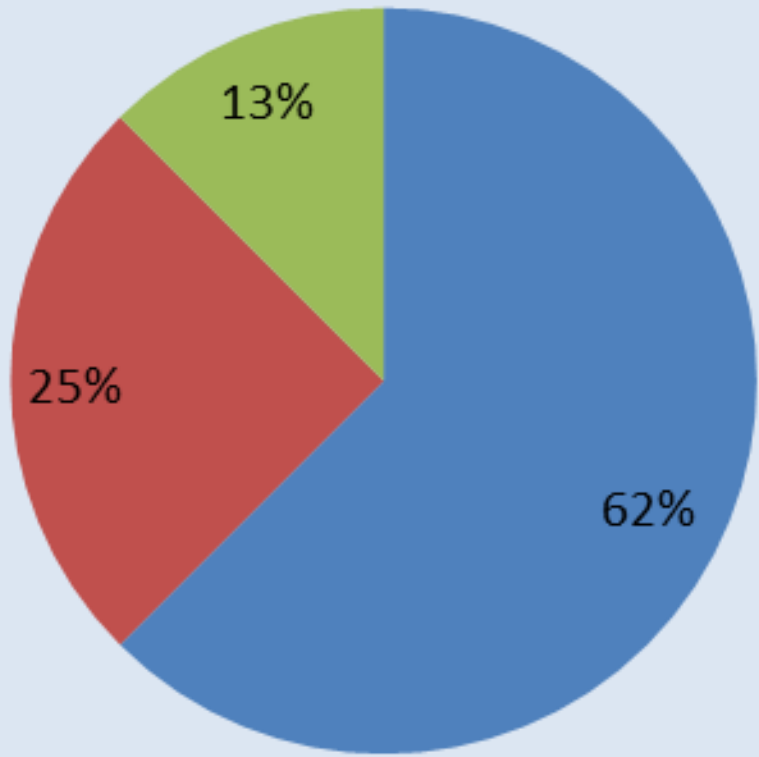


Conclusions: This is a general methodology that can be applied to any early phase oncology combination for which combo preclinical antitumor and clinical safety data are available.



Key Application Area

Drug Development Decision-making



Key Application Sub-areas

- Dose/Schedule selection
- Outcome predictions
- Safety assessment

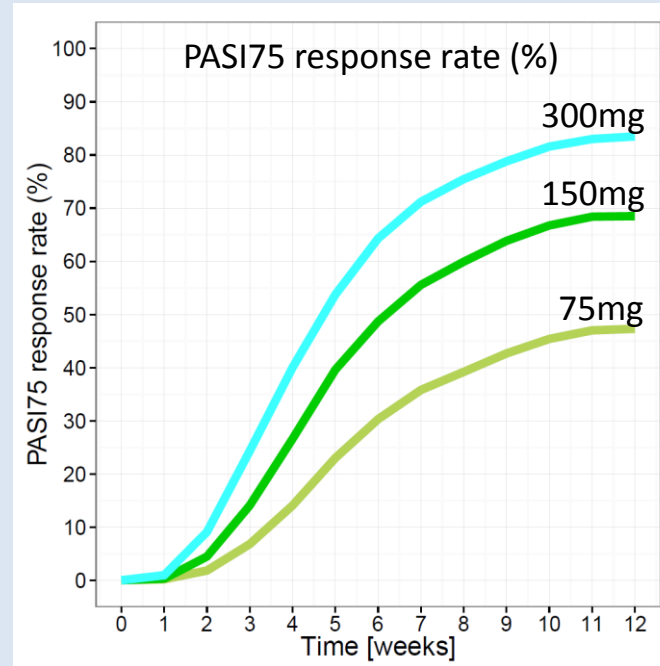
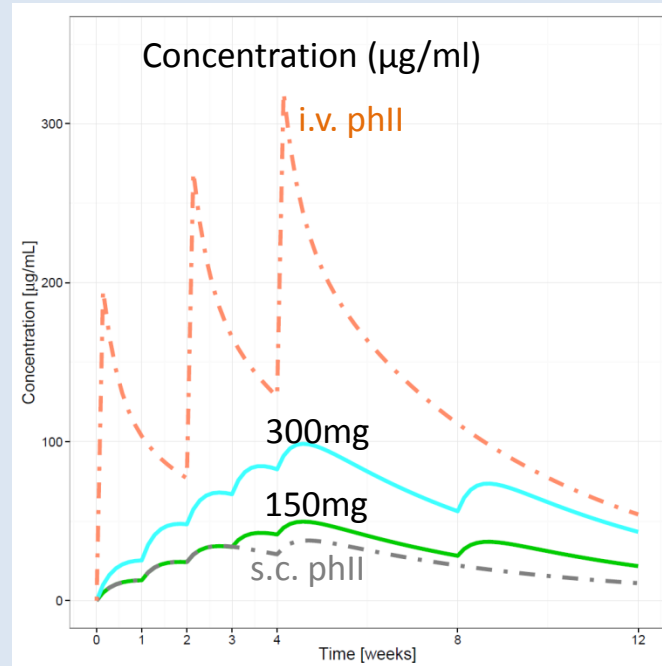
Model-based selection of the secukinumab dosing regimen in psoriasis

Key Question: What is the optimal dosing regimen to be used in phase 3?

Data - Data from five phase I/II studies was integrated across different doses, regimens, and routes of administration

Model - Population-PK/PD models were incrementally built, evaluated, and updated with accruing data

Results - Phase 3 studies confirmed the predicted efficacy for the 150mg and 300mg regimens. After phase 2 this model allowed to select optimized regimens based on predicted response



Conclusions: Model-based integration of phase I/II data allowed the selection of two dosing regimens for phase III which had not been tested previously. Phase III confirmed the positive benefit-risk for those regimens and the regimens were approved.

[1] Sander et al. Model-based development of the secukinumab dosing regimen [...]. PAGE meeting 2016.

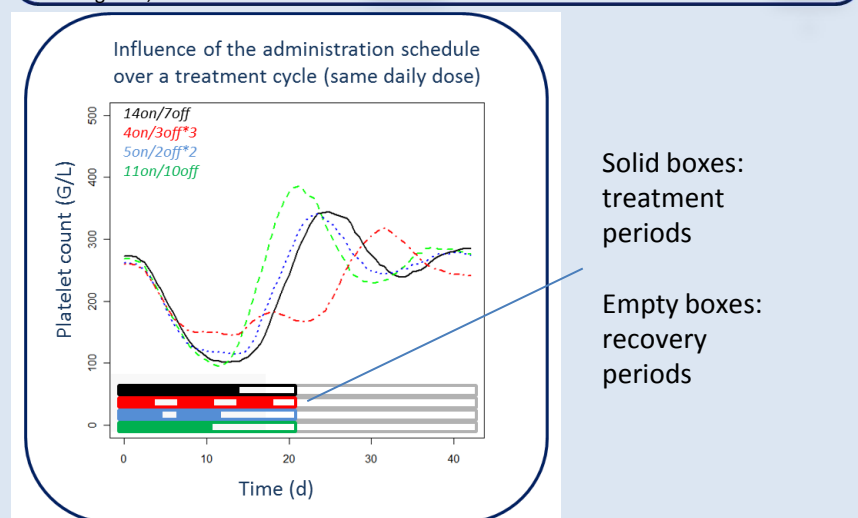
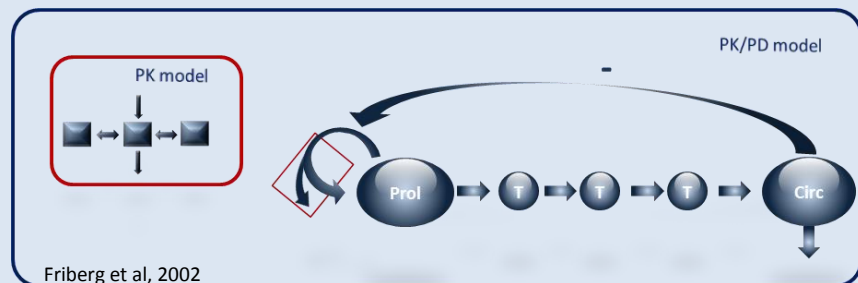
[2] Langley et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med.* (2014) 371(4):326-38.



Determination of the optimal administration schedule using a PK/PD approach

Key Question: How to predict an optimal administration schedule early in clinical development?

- **Data:** Concentration-time profiles for 49 patients, after oral and IV administration (*qd*, *bid*, *tid*, 6 different weekly adm. schedules) Platelet-time profiles for 35 patients, after oral administration (*bid*, *tid*, 4 administration schedules)
- **Modeling / Analysis Method:** Sequential PK/PD modeling
- **Results:** A semi-mechanistic PK/PD model was able to describe the available data across administration schedules and doses
- **Simulation:** For a similar exposure over a 21-days treatment cycle, it was shown that the administration schedule 4 days on treatment and 3 days off treatment, every week, was the safest



Conclusions: This work shows a clinical application of early PK and PKPD modeling of a new HDACi as an influential development tool for the selection of an optimized administration schedule. A wide range of simulation conditions were evaluated, and an optimized administration schedule was determined. This treatment schedule was clinically evaluated after a protocol amendment and a new MTD was defined with a 30% higher dose intensity.



PK/PD Modeling of GPR40 Agonist MK-8666 Proof of Concept Data to Inform Clinical Decisions

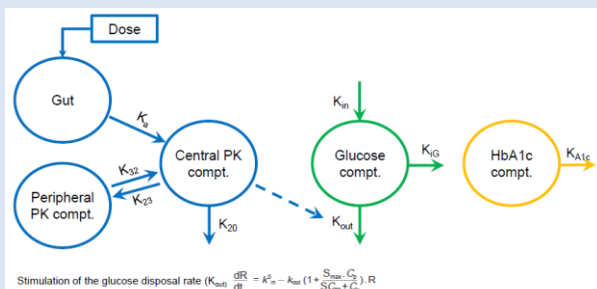
Key Question: What is the optimal dose range for a Ph2B study and does the compound have sufficient differential potential to DPPiVs?

Data:



Modeling:

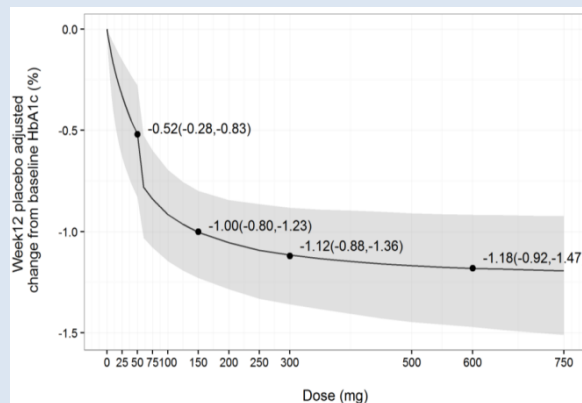
- An indirect response PK-FPG model was based on the pop PK model and FPG data from the clinical POC study.
- A published FPG-HbA1c relationship¹ was used to extrapolate MK-8666 FPG response to 12-week HbA1c



Results (Dose Range):

- Robust glucose- and HbA1c-lowering effects are predicted at Week 12 at doses of 150 mg and greater
- At doses of >250-300 mg, the predicted additional reduction in glycemic response is attenuated

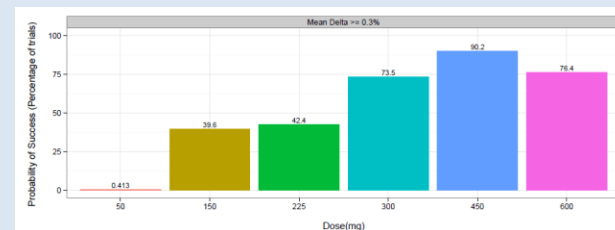
Predicted Week 12 placebo-adjusted reductions from baseline in HbA1c



Simulations (differentiation):

- A potential clinically efficacious dose of 300 mg had the highest probability for a superior glycemic efficacy in comparison to DPPiV inhibitors retaining an adequate safety margin

Probability of a dose of MK-8666 to demonstrate a placebo- and baseline-adjusted mean difference of $\geq 0.3\%$ in A1C at Week 12, compared with a DPP-4 Inhibitor



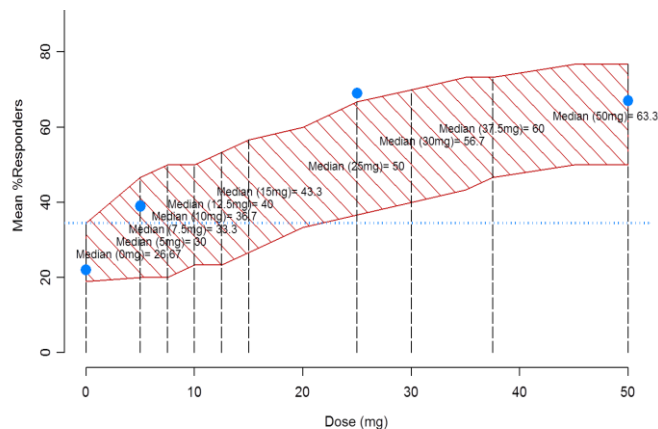
Conclusions: Integration of modeling and simulation with team strategy allowed extrapolation of 2-week proof-of-concept study results to 12-week HbA1c response. The predicted dose-HbA1c curve facilitated decisions on dose selection with a differentiation potential for a proposed Phase IIb study.



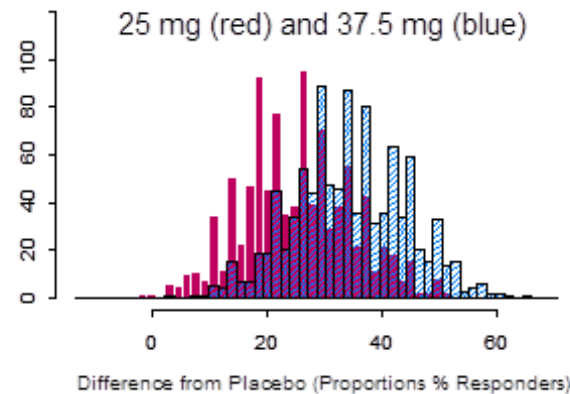
Modeling and simulation to support Naloxegol dose selection for Phase 3 studies

Key Question: What is the optimal dose of Naloxegol and best trial design for clinical phase III trial to confirm efficacy and safety?

Dose-response relationship developed with phase 2b data



Simulated distribution of mean difference from placebo



Methods: A longitudinal mixed-effects negative binomial model was developed in 185 patients from phase 2b study to characterize the relationship between naloxegol dose and the weekly probability of being a responder. In addition, a model for the time to study discontinuation (dropout) was also developed, and the two models were used together to predict responder rate in the study.

Conclusions:

The exposure-response analysis at Phase II demonstrated the 25 mg was an effective dose with updated primary endpoint. Model-based simulations suggested that doses of 12.5 mg and higher would provide a promising clinical benefit over placebo.



Model to inform and speed early development of an SGLT2i

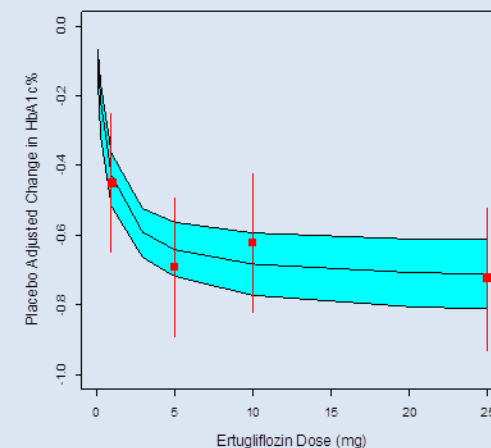
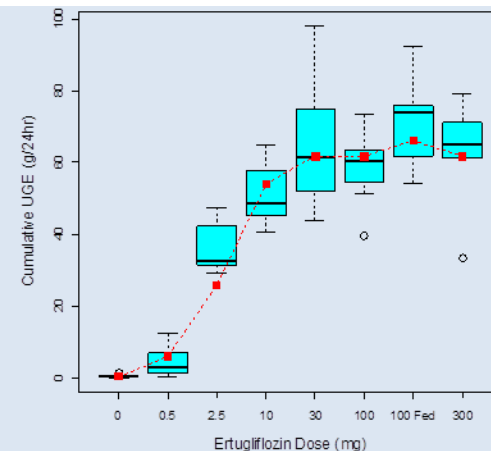
Key Question: Can we integrate target, physiology and disease in a comprehensive manner to predict efficacy in Type 2 Diabetes PoC Trial from healthy volunteers target engagement data?

Data – Published data on other SGLT2i compounds, target engagement PK/PD for lead selection, physiologic understanding of mechanism of action were used in the development and application of systems pharmacology model.

Modeling / Analysis Method - Physiologically based representation of competitive SGLT2 inhibition in PhysioLab to account for the effect on glucose reabsorption in the proximal tubule, tuned with literature data for PK and UGE for healthy and T2DM subjects.

Results – Validated model was tuned with PK and biomarker response in healthy subjects FIH (single dose) and was able to predict efficacy as observed in a 12-week Ph 2b diabetes trial.

Inference - The model provided a quantitative link between the mechanism of action biomarker (UGE) and long term end-points (Hb1AC and WT) across different populations (healthy & patients).



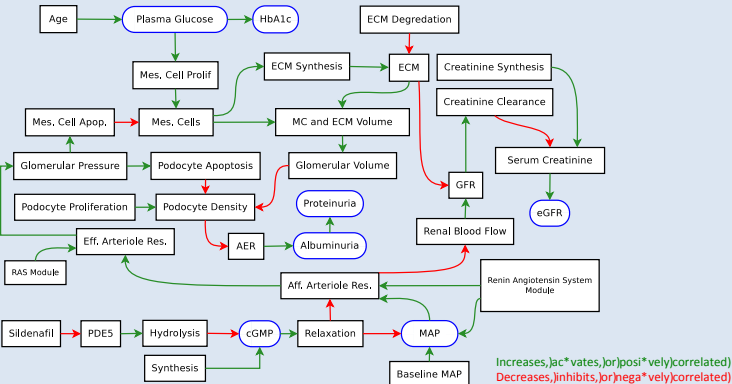
Conclusions: The model successfully predicted efficacy in T2DM subjects from observed FIH study data, results of this effort helped complete FIH to end of Phase 2 within 14 months.



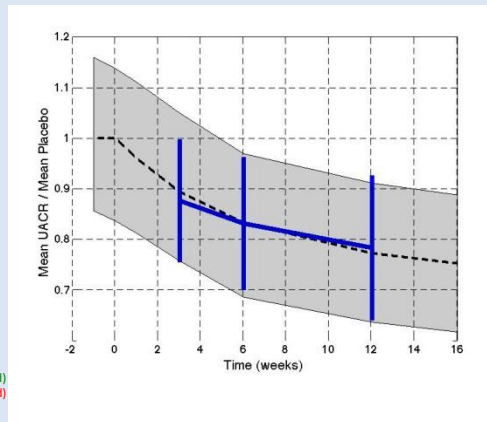
Analysis and Translation of Phase II data to Registration Endpoints in Chronic Kidney Disease

Key Question: For a novel PDE5i for chronic kidney disease (CKD), for this mechanism, how will phase II outcomes translate to registration endpoints using a Systems Pharmacology Model?

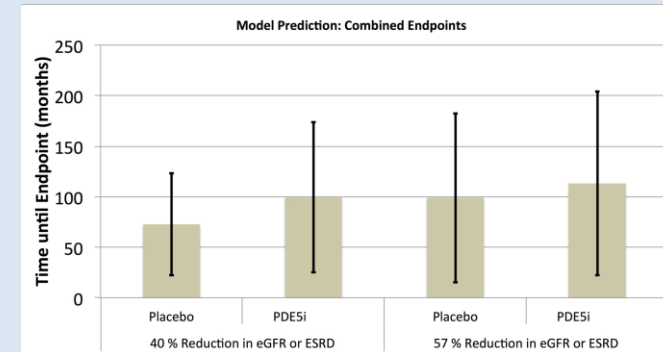
Systems Model Representation of Key Physiology (in collaboration with Institute for Systems Biology, Moscow).



Constrain Model Against Phase II data



Use revised model to predict potential phase III endpoints.



Inference

- Data driven approaches failed to establish a relationship between UACR and Phase III endpoints due to high variability. Systems modeling approach predicts modest magnitude of improvement in disease, and indicates which endpoint is preferential.

Conclusions: By application of known physiology, and incorporation of diverse data sets the systems modeling added significant value beyond traditional meta-analytical approaches

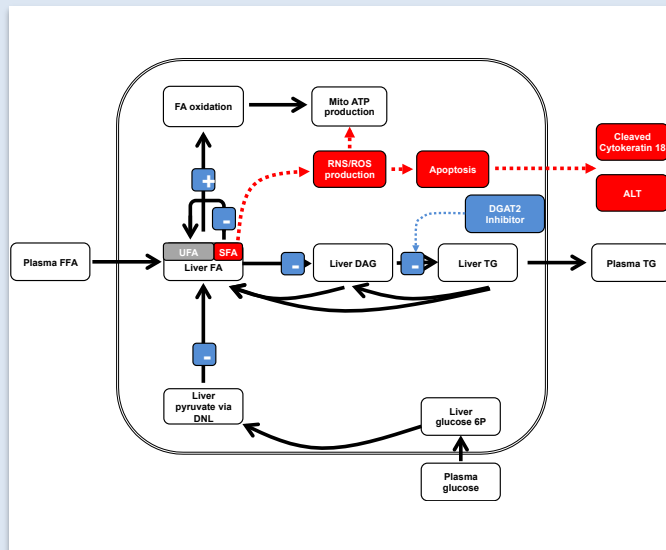


Predicting the Potential Efficacy for a Novel Treatment for Non-Alcoholic Fatty Liver Disease

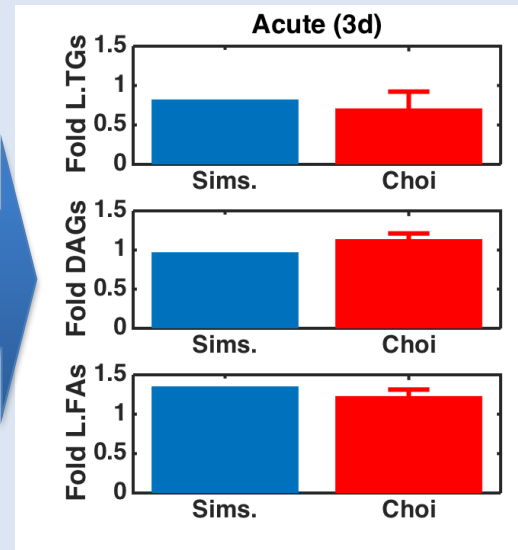
Drug Development
Decision-making

Key Question: Can we use a mechanistic model to project efficacy for a treatment for fatty liver disease given that early clinical studies cannot directly measure changes in liver fat (L.TGs)?

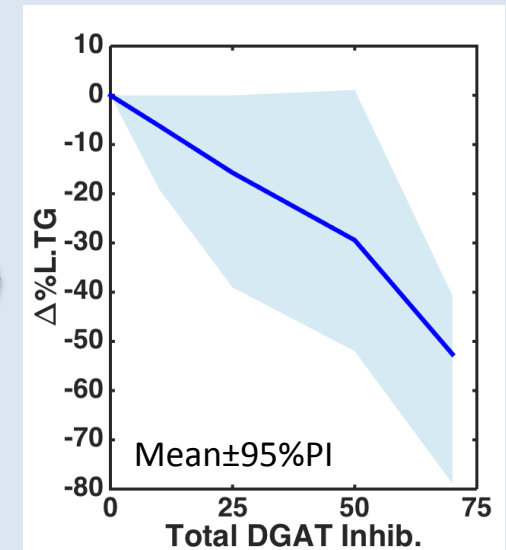
Systems Pharmacology Model (NAFLDsym™)



Calibration Using Pre-clinical Data



Projected Change in Liver Fat in a Phase II Clinical Study

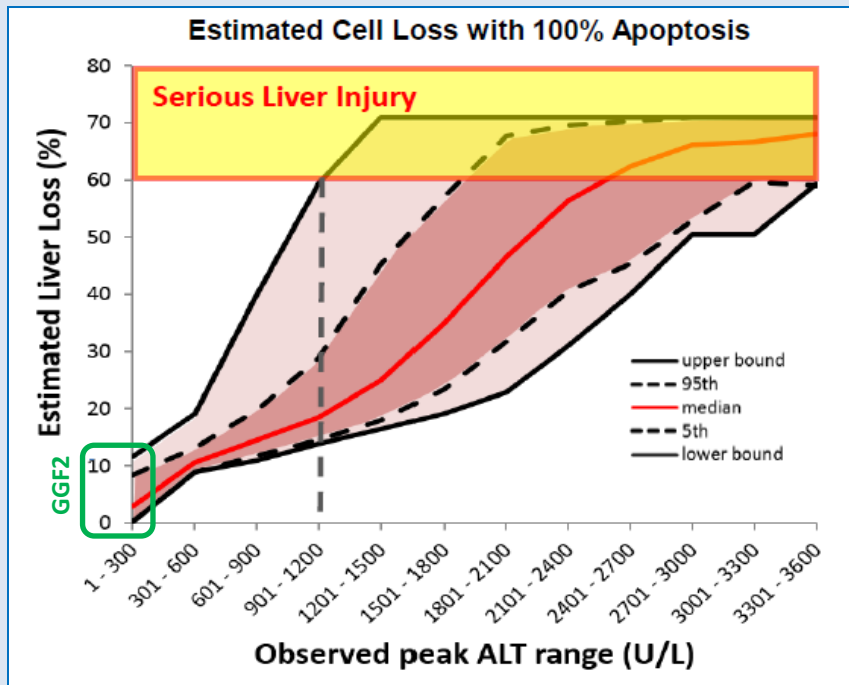


Conclusions: The model quantified both the therapeutic potential for the novel treatment and showed some of the variability in response. In future applications, the model can be used for testing questions about clinical design (e.g., inclusion/exclusion, duration, dose).



Assessment of liver safety risk in Phase 1 GGF2 clinical trials

Key Question: Can mathematical modeling determine the extent of hepatocyte loss and effect on serum bilirubin in 2 subjects who met Hy's Law Criteria in clinical trials of GGF2 although peak ALT was <300 U/L?



Inference:

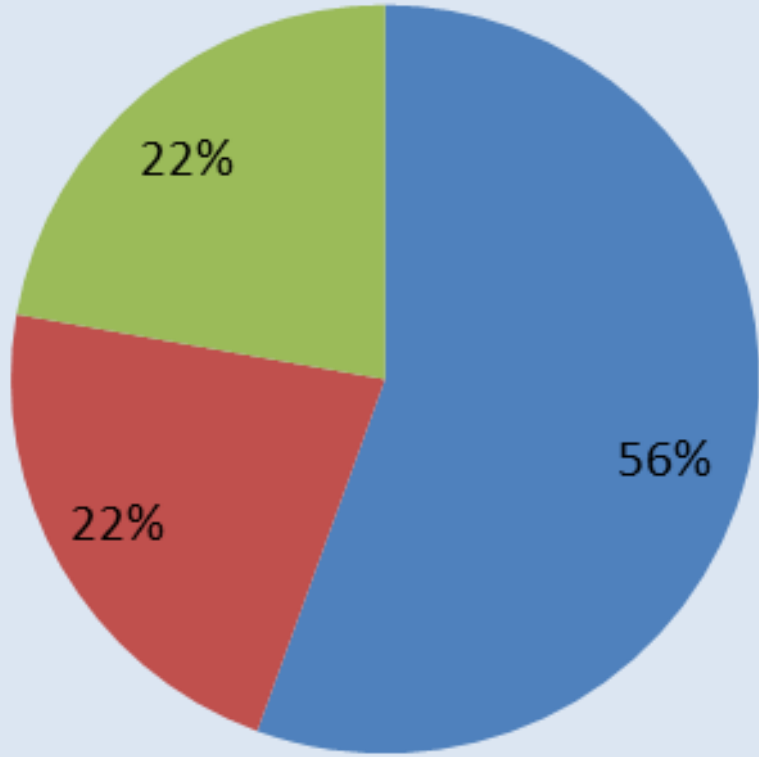
ALT elevations in GGF2-treated subjects are comparable to those observed with heparins, which do not cause clinically significant liver injury when taken as directed, and where hepatocyte loss is predicted to be <16% in healthy volunteers. Clinically serious liver injury (>60% estimated hepatocyte loss) is possible-likely when peak ALT >1200-1800 U/L.

Conclusions: Traditional and novel biomarker analyses together with DILIsym analysis suggest that the 2 subjects with simultaneous elevations in serum aminotransferases and total bilirubin observed in the Phase 1 GGF2 clinical trials should not be considered typical Hy's Law Cases



Key Application Area

Regulatory Decision-making



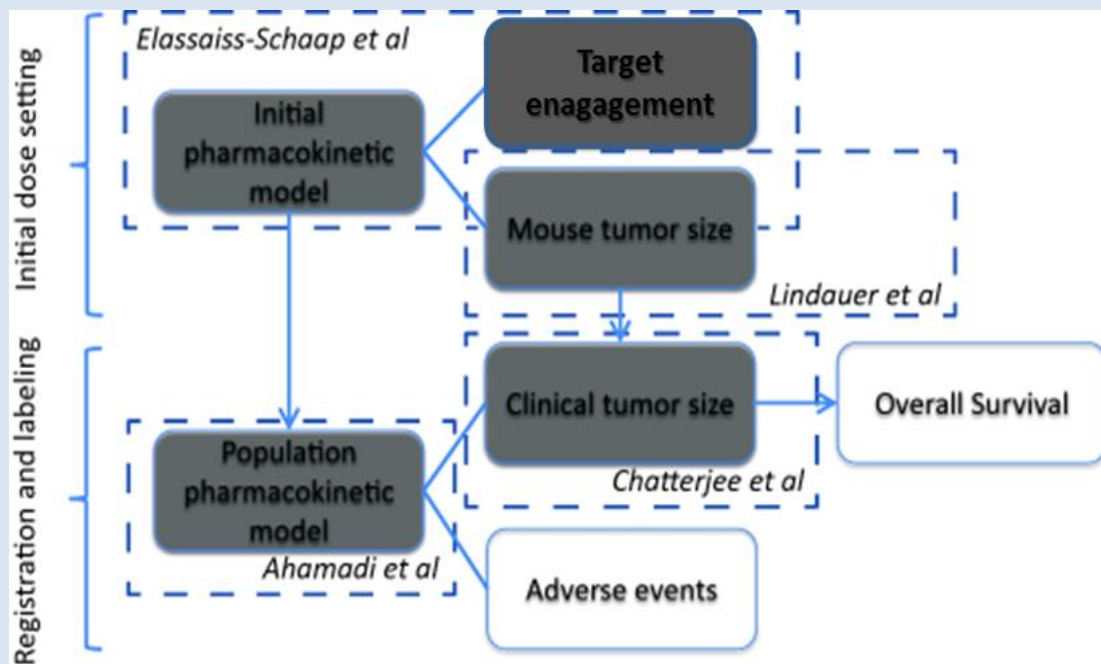
Key Application Sub-areas

- Dose/Schedule Justification
- Risk/Benefit evaluation
- Label claims

M&S drove the selection of Pembrolizumab efficacious dose of 2 mg/kg

- **Key Question:** What is the efficacious dose and schedule of Pembrolizumab? Are intrinsic/extrinsic factors impacting dose/schedule for subpopulation?

- **Data:** Preclinical and early clinical PK and tumor-size
- **Modeling Approach:** Translational PK-tumor-size and early clinical PK (TMDD) analysis guided selection of 2 mg/kg in later studies
- **Results:** Exposure vs tumor-size as well as safety showed flat relationship between 2 and 10 mg/kg demonstrating that the dose of 2 mg/kg Q3W is at the plateau of maximal response.



Inference: modeling and simulations demonstrated flat dose/exposure-response over 2-10 mg/kg

Conclusions: Translational, Clinical PK and Exposure-Response Analyses demonstrated that the lowest dose of pembrolizumab achieving a maximal response would be 2 mg/kg Q3W. This dose and regimen was subsequently approved for patients with advanced melanoma

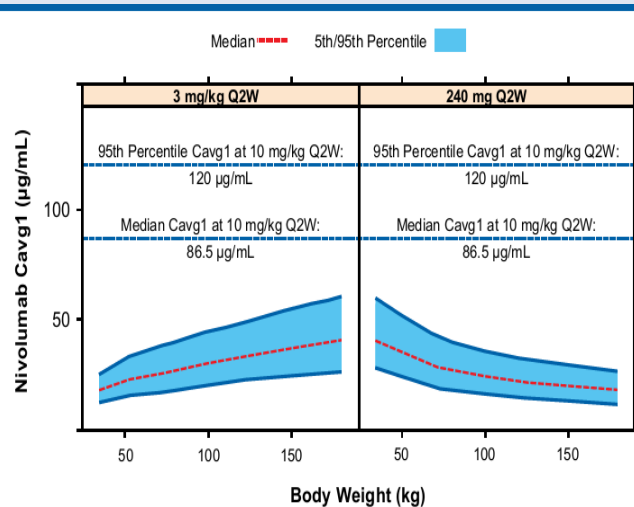


Quantitative Clinical Pharmacology analyses conducted in support of 240 mg nivolumab flat dose approval

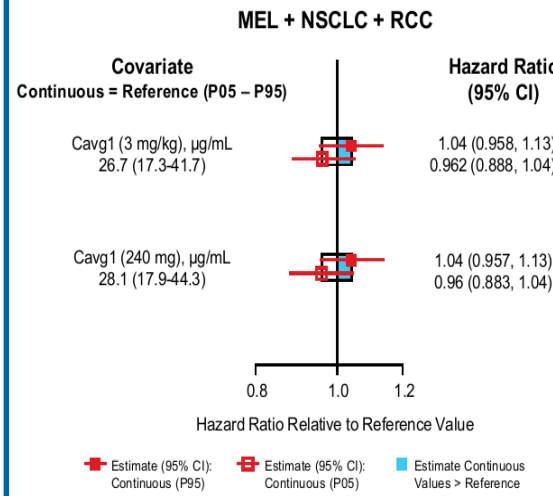
Regulatory
Decision-making

Key Question: Can quantitative clinical pharmacology approaches be used to switch body weight based dosing (3 mg/kg Q2W) to flat dose (240 mg Q2W) of nivolumab?

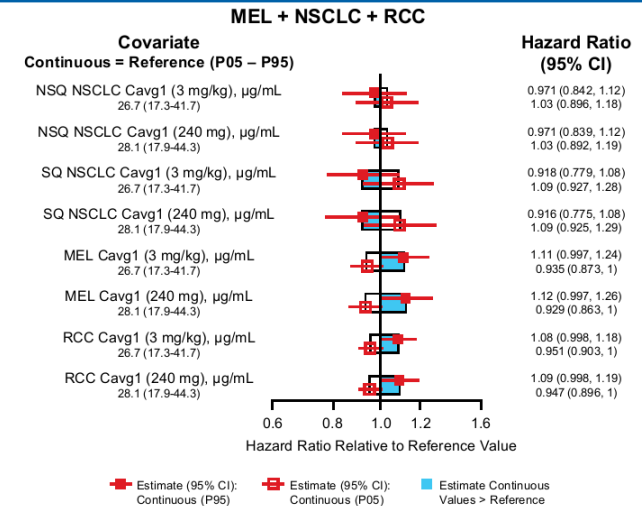
PK by Body Weight



Safety Prediction



Efficacy Prediction



Inference

- Based on population pharmacokinetic modeling, established flat exposure-response relationships for efficacy and safety, and clinical safety, the benefit-risk profile of nivolumab 240 mg Q2W was comparable to 3 mg/kg Q2W.

Conclusions

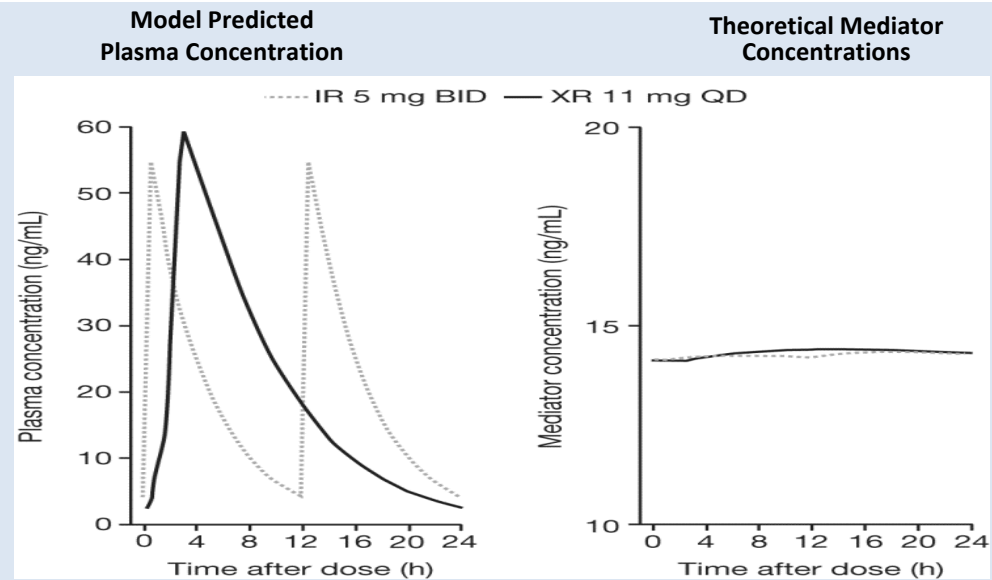
- The quantitative clinical pharmacology approach provided evidence for regulatory decision-making on dose modification, obviating the need for an independent clinical study.



Tofacitinib XR –Achieve Regulatory Approval for a new formulation/dosing regimen without a Phase 3 Study

Key Question: Can QP paradigm support the conclusion of similar efficacy and safety of a once daily extended release (XR) formulation of tofacitinib as that of the approved immediate release (IR) formulation, without confirmatory evidence from a Phase III study?

- **Data:** Clinical (Phase II dose-ranging studies of the IR formulation) and nonclinical (murine models of efficacy).
- **Modeling:** Series of nonlinear mixed effect models built using validated clinical endpoints.
- **Results:**
 - AUC (or C_{av}) was the most relevant PK predictor of tofacitinib efficacy.
 - Consistent with tofacitinib’s indirect mechanism of action, fluctuations in concentration-time profile over the course of a dosing interval were not expected to be clinically meaningful and therefore C_{min} differences between the two formulations were not important to the efficacy of tofacitinib, given the AUC equivalence.
- **Inference:** Innovative strategy where PK/PD based analyses in conjunction with PK data formed the basis of benefit/risk assessment of the XR formulation. On the basis of E-R analyses and PK data showing equivalence of AUC between the formulations, tofacitinib XR was approved by US FDA in February 2016.



Conclusions: The analyses illustrate the potential of robust dose-response studies and E-R relationships to facilitate efficient drug development of alternate formulations and provide sufficient evidence to obviate the need of Phase 3 trials



Pharmacometric analysis of phase 3 studies results to influence regulatory decision making for naloxegol

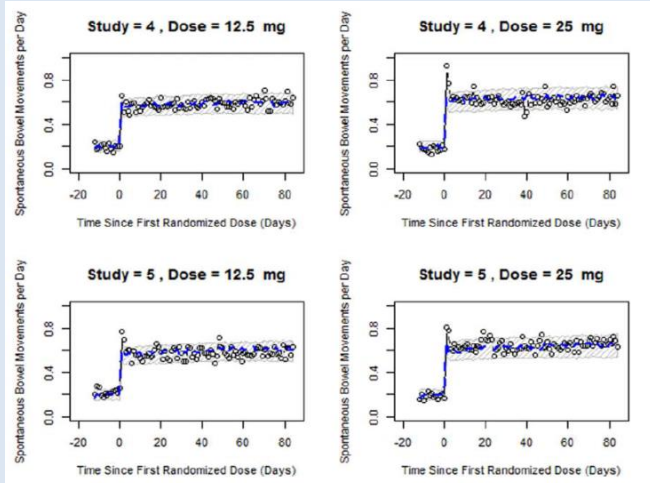
Key Question: Does lowering the dose from 25 to 12.5 mg naloxegol provide benefit in patients with opioid-induced constipation?

Data: two identical phase III studies were conducted and the response rates were statistically significantly higher with 25 mg of naloxegol than with placebo for both studies, but the 12.5 mg of naloxegol was only found to be statistically effective ($\alpha=0.05$, $p=0.202$ and $p=0.015$) in one of the phase 3 trials

Observed and population mean predicted responder rates

Treatment group	Observed responder rate, % (90% CI)	Population mean predicted responder rate, % (90% PI)
Placebo	29.5 (25.9–33.1)	32.9 (28.7–37.5)
Naloxegol 12.5 mg	38.1 (34.3–41.9)	42.7 (36.5–47.2)
Naloxegol 25 mg	41.9 (38.1–45.8)	43.0 (36.7–46.9)

Daily spontaneous bowel movements



Methods: Exposure-efficacy model integrating dropouts was developed using spontaneous bowel movements (SBM) data from 1,331 patients in two phase 3 pivotal trials. Number of SBMs was characterized by a longitudinal non-linear mixed-effects logistic regression dose-response model. Dropout (incidence of diary entry discontinuation) was described by a time-to-event model.

Conclusions: Exposure-response analysis at phase III demonstrated the 12.5 mg dose could provide a clinical benefit over placebo with comparable efficacy to the 25 mg dose. The conclusion was accepted by regulatory and presented in the naloxegol's package insert

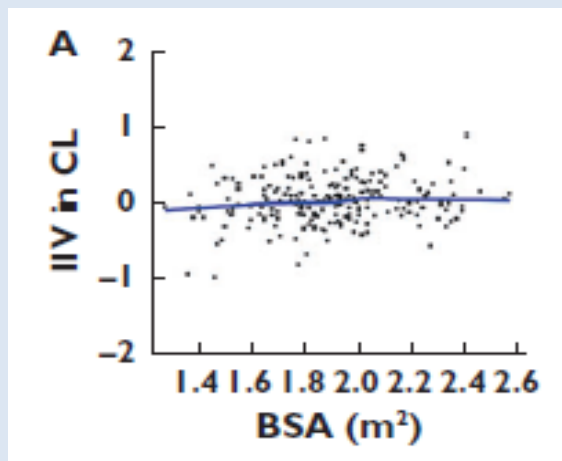


Switch from BSA-based to fixed dosing simplified dosing guidance and clinical development

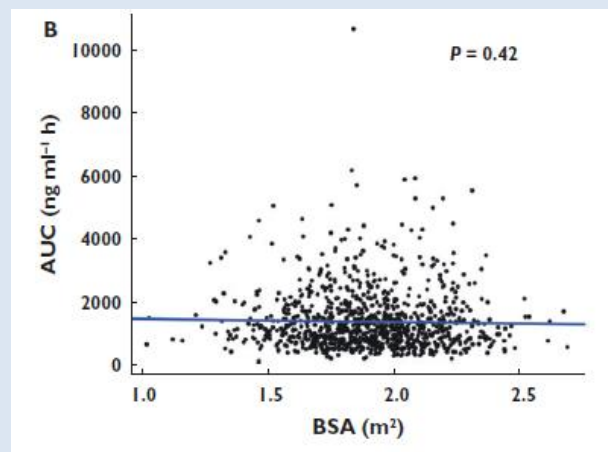
Key Question: Can modeling guide switching from body surface area-based to fixed dosing without conducting a standalone study to compare fixed dosing vs BSA based dosing?

Data/Method: Data from 226 adult patients with multiple myeloma, lymphoma, or solid tumors in four phase 1 studies was analyzed using NONMEM version 7.2

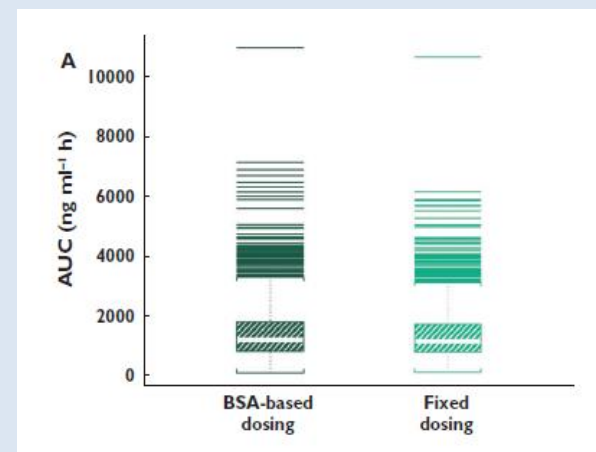
Results (N=226)



Simulations (N=1000)



Simulations (N=1000)



Inference: median AUCs were similar after BSA-based and fixed oral dosing

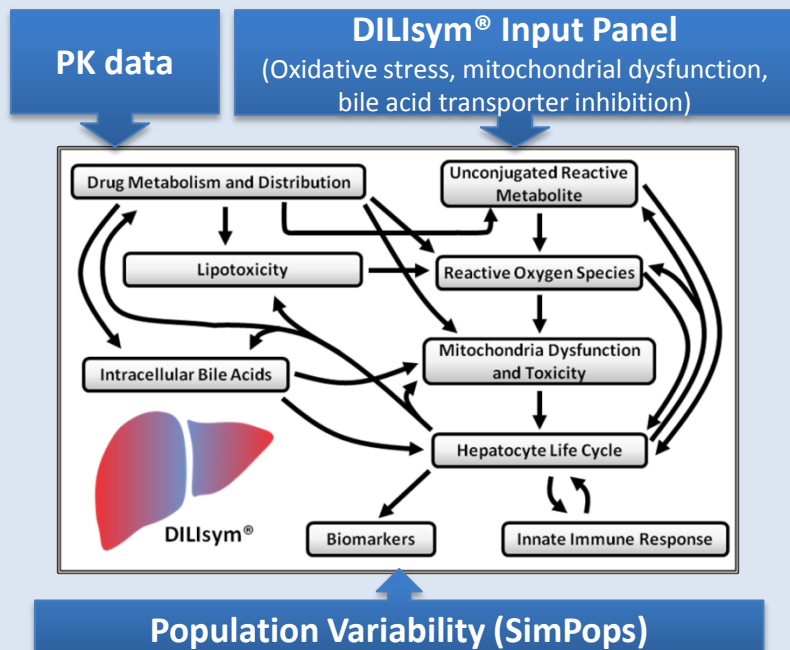
Conclusions: Clinical development switched posology from BSA-based to fixed dosing, simplifying capsule strength manufacture and dosing in global clinical trials. Fixed dose of 4 mg was subsequently used in phase-3 TOURMALINE MM1 study that formed basis for approval of ninlaro (Ixazomib) by FDA and EMA.



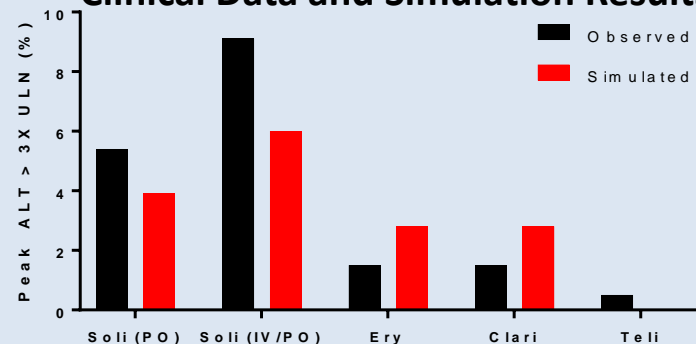
Investigation of Underlying Mechanisms of Liver Enzyme Elevations by Macrolides

Key Question: What are the underlying mechanisms of observed liver enzyme elevations for solithromycin and other macrolides?

DILIsym[®] Mechanism-Based Modeling



Clinical Data and Simulation Results



Compound	Soli	Ery	Clari	Teli
Predicted Hy's Law cases	0%	0%	0%	0%
Predominant Mechanism	ETCi	BAi	ETCi	-
Minor Mechanism	BAi	OS	BAi	BAi

Soli: solithromycin, Ery: erythromycin, Clari: clarithromycin, Teli: telithromycin, ETCi: mitochondrial electron transfer chain inhibition, BAi: inhibition of bile acid transporters, OS: oxidative stress

Inference: Mechanisms for ALT elevations vary among macrolides and solithromycin is similar to clarithromycin in this regard

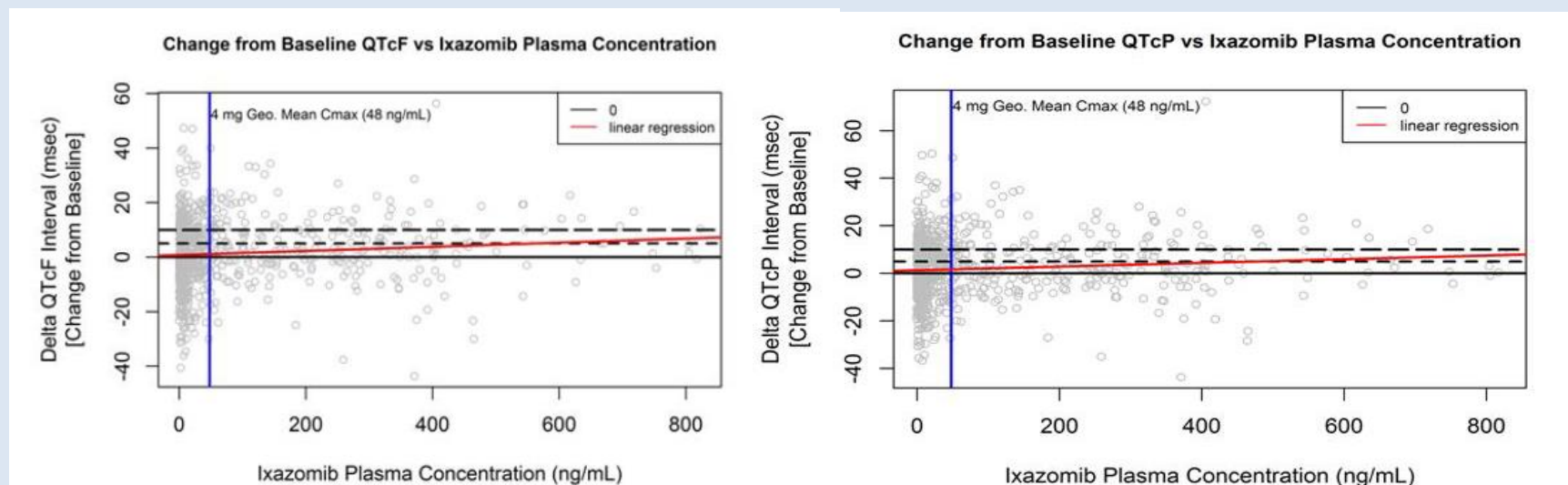
Conclusions: Quantitative systems toxicology modeling reasonably predicted the incidence of ALT elevations for different macrolides and characterized underlying mechanisms. The simulation results were presented to the FDA Advisory Committee for solithromycin



Concentration–QTc modeling of phase 1 data to obviate need for a dedicated clinical QTc study

Key Question: Can an integrated non-clinical and clinical risk assessment on the QTc interval for Ixazomib obviate the need for a dedicated clinical QTc study?

- Pharmacokinetic–matched triplicate electrocardiograms (ECGs) were collected in four clinical phase I studies of intravenous (0.125–3.11 mg/m², N=125, solid tumors/lymphoma) or oral (0.24–3.95 mg/m², N=120, multiple myeloma) ixazomib.
- The relationship between ixazomib plasma concentration and heart-rate (HR) corrected QT using Fridericia (QTcF) or Population (QTcP) methods was analyzed using linear mixed-effects models with fixed effects for day and time.



- At an ixazomib plasma concentration of 200 ng/mL (approximately four times the geometric mean Cmax at the 4 mg dose), the upper limits of the 90 % CIs for the mean Δ QTcF and mean Δ QTcP were well below 5 ms (the regulatory threshold as per ICH E14 guidelines)

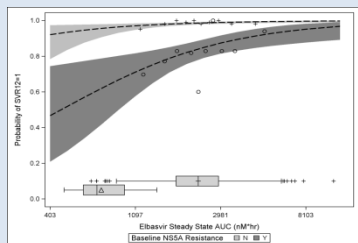
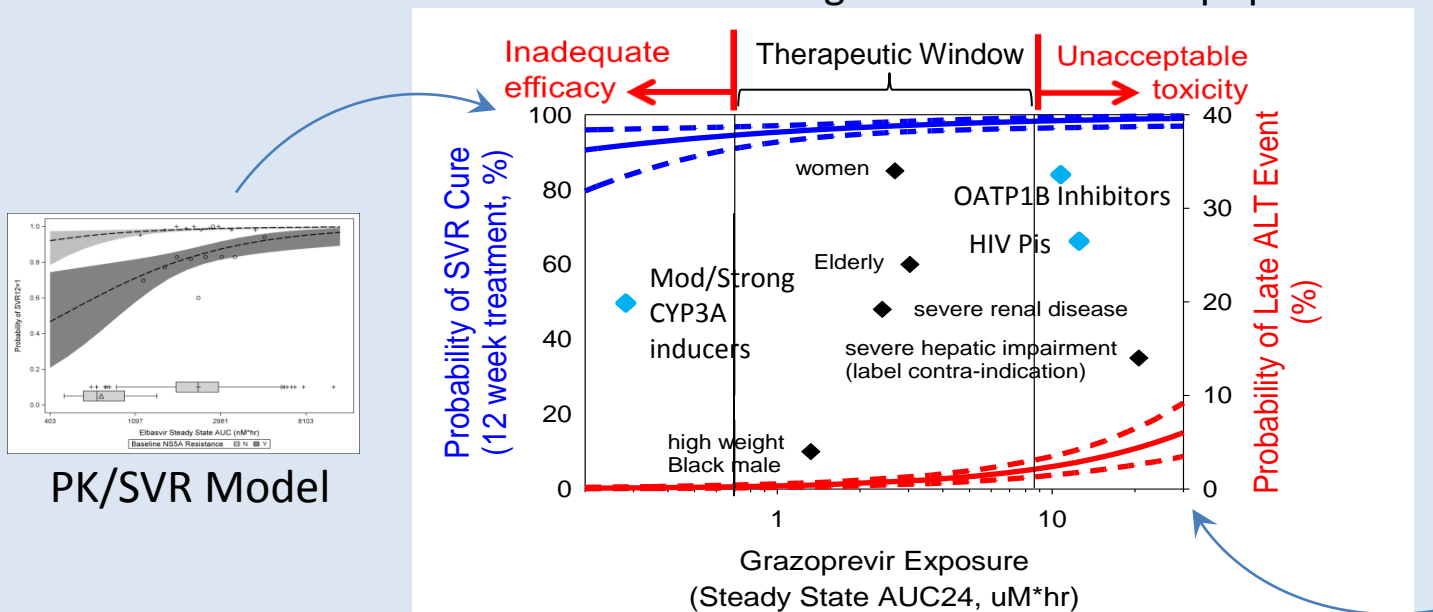
Conclusions: Ixazomib has no clinically meaningful effects on QTc or HR. Integrating preclinical data and concentration–QTc modeling of phase 1 data was accepted in lieu of a dedicated clinical QTc study. Ixazomib (ninlaro) was approved by FDA on Nov 20, 2015 and results from this analysis were included in the USPI of Ixazomib.



Limited label restrictions for drug interactions and demographics based on established therapeutic window

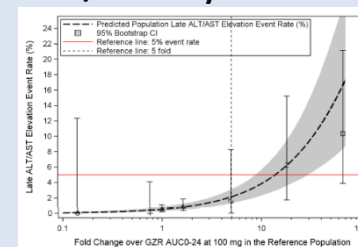
Key Question: Which drug interactions and demographic factor effects are clinically relevant and require dose adjustments or contraindications in the drug label?

Data: ~2000 Patient Data + ~25 Phase I Drug Interaction or Sub-population Studies



PK/SVR Model

PK/Safety Model



Inference: Most drug interactions and demographic factors that effect drug exposure resulted in exposures within the therapeutic window, and therefore not clinically relevant.

Conclusions: PK/PD analyses for safety and efficacy provided an integrated understanding of exposure-response to establish the therapeutic bounds. Despite several drug interactions and demographic effects, the therapeutic bounds demonstrated that few effects were clinically relevant. The drug label had limited contraindications for drug interactions and demographics.



PBPK modeling to support dosage recommendations for naloxegol drug-drug interaction labeling

Regulatory
Decision-making

Key Question: How should naloxegol be prescribed to avoid potential drug-drug interactions?

PBPK development



Verification



Prediction

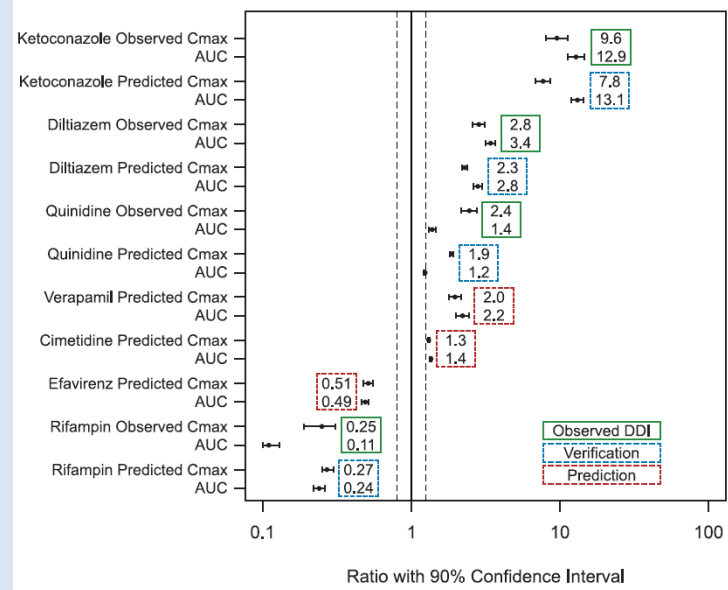
Developed with in vitro/in vivo information

Verified with clinical DDI studies

Predicted for untested clinical DDI cases

Method: Full PBPK models were developed to predict the drug-drug interaction (DDI) potential for naloxegol.

Results: Based on the simulations, weak CYP3A inhibitors are expected to have minimal impact on naloxegol exposure in routine clinical use, whereas moderate CYP3A inducers may reduce naloxegol exposure by 50%.

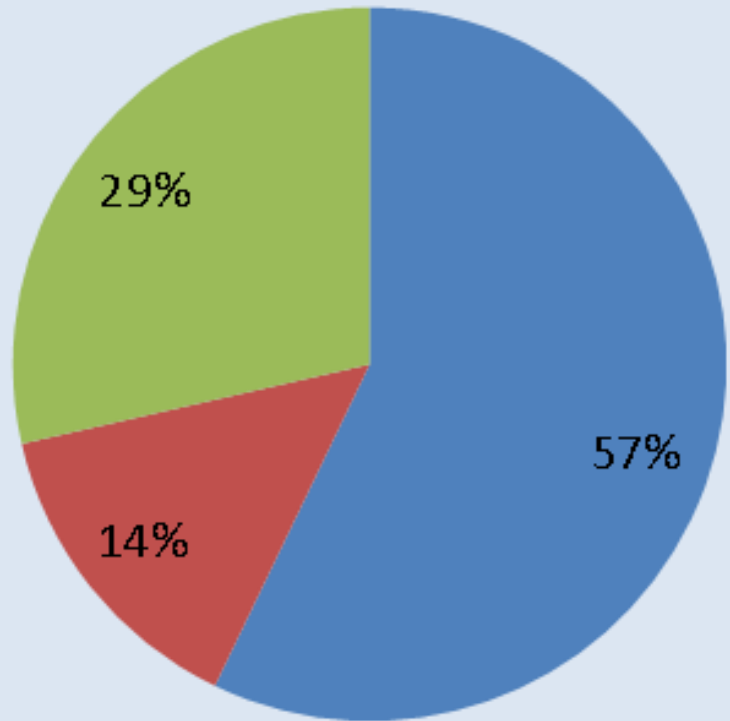


Conclusions: In combination with clinical drug-drug interaction results, the PBPK model predicted results provided comprehensive dosage recommendations for naloxegol in the package insert.



Key Application Area

Therapeutic Use & Special Populations



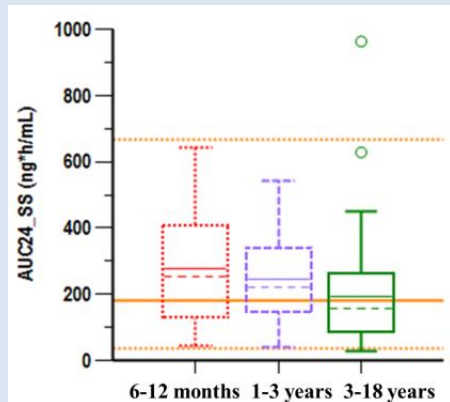
Key Application Sub-areas

- Pediatric dose setting
- Drug-Drug interactions
- Precision Medicine

Key Question: How to determine the starting dose in children suffering from chronic heart failure?

- **Data:** PBPK model qualified in adults.
- **Modeling / Analysis Method :** Plasma concentration-time profiles of ivabradine were simulated in each age class (i.e. 6-12 months, 1-3 years, and 3-18 years) at SS after repeated ivabradine oral administrations of 0.1 mg/kg b.i.d. using the PBPK model.

Results



Yellow lines: Median (solid) and 90% CI (dotted) AUC in adults

Age subsets	Dose units	Initial dose
6-12 months	mg/kg	0.02
1-3 years	mg/kg	0.05
3-18 years ≤ 40 kg	mg/kg	0.05
3-18 years > 40 kg	mg	2.5

- **Inference :** The criterion for selecting the doses was to achieve the same ivabradine exposure as in adult (based on the initial assumption that the PK/PD relationship is similar between children and adults).

Conclusions: This work emphasizes the importance of modeling and simulation for internal decision-making such as the design of clinical studies in pediatric populations. With this work it was possible to determine the starting dose in children and to define a lower dose in younger children since they presented a higher exposure compared to adults

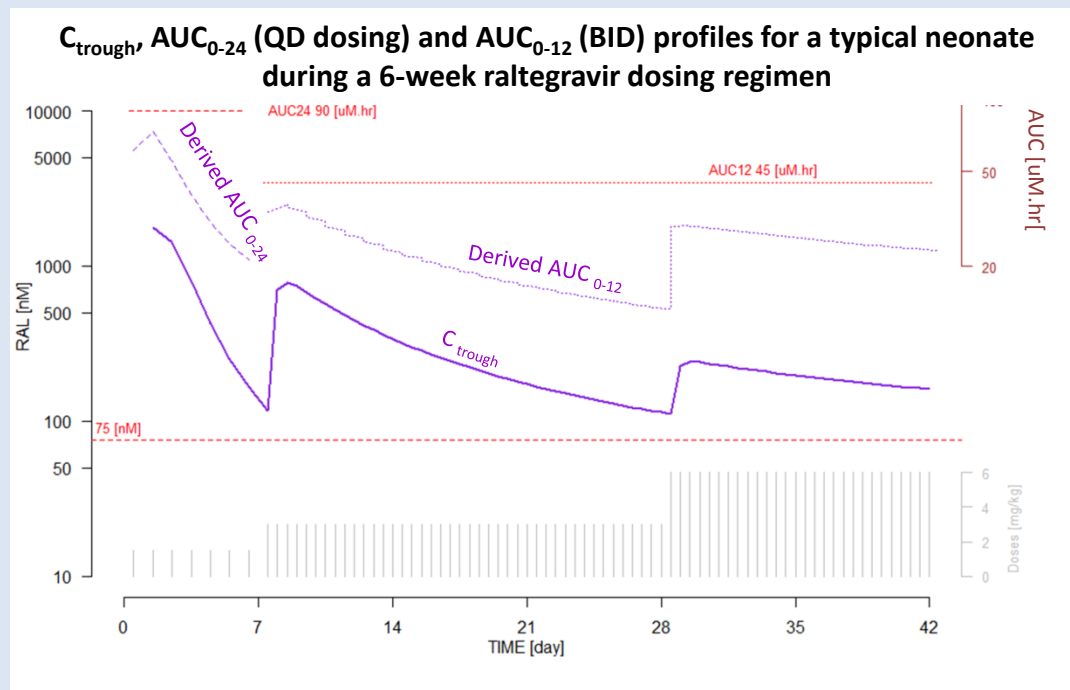


Adaptive trial design to define Raltegravir dosing regimen to treat neonates from birth up to 6 weeks of age

Therapeutic Use & Special Populations

Key Question: How to address the dramatic increase of clearance due to UGT-1A1 maturation in a 6-week dosing regimen for neonates?

- **Data** - Limited PK data of 6 neonates only, in combination with infant PK data, were sufficient to describe UGT-1A1 maturation
- A 6-week dosing regimen was designed accounting for efficacy and safety PK criteria. Two dose regimen changes are needed to account for the dramatic changes of raltegravir clearance
- **Result** - The regimen was applied in a second cohort of the study and shown to be adequate



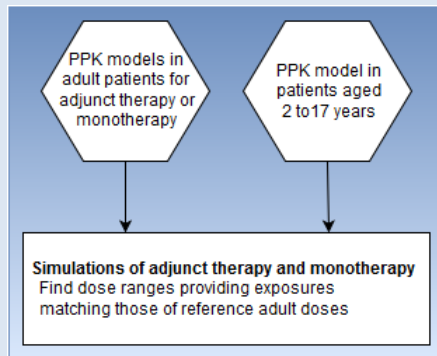
Conclusions: The dramatic increase in raltegravir clearance as the result of UGT-1A1 enzyme activity in neonates requires 2 dose changes over the first 6 weeks of life to meet efficacy and safety PK criteria.



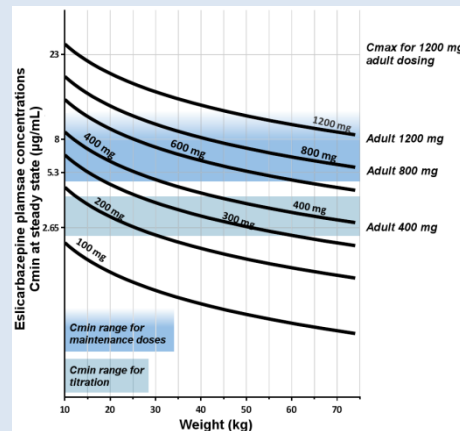
Extrapolation Strategy for ESL Dosing in Pediatric Patients with Partial-Onset Seizures (POS)

Key Question: Which doses of Eslicarbazepine Acetate (ESL) provide exposures in 4-17 y patients with POS that are similar to those determined to be safe and effective in adult patients for ESL adjunct therapy or monotherapy?

Model-based strategy



Target matched exposures



Proposed adjunct therapy or monotherapy dose by body weight range

Body Weight	Titration Dose (mg/day)	Maintenance Dose (mg/day)
< 11 kg	200	300 to 400
11 to 21 kg	200	300 to 500
22 to 31 kg	300	400 to 700
32 to 38 kg	300	600 to 800
>38 kg	400	800 to 1200

Inference: Based upon the similarity of POS in pediatric patients aged ≥ 4 y and adults[1], pediatric ESL doses could be extrapolated from adult exposures using model-based simulation [2].

Conclusions: Extrapolation obviated the need to conduct a US-based clinical trial in pediatric patients aged ≥ 4 y. Benefits of this strategy are to reduce the number of pediatric patients exposed to clinical trials and to allow for earlier availability of ESL for clinical use in pediatric patients.

[1] US FDA. FDA update: anti-epileptic drug efficacy in adults can be extrapolated to pediatric patients. April 6, 2016. AAP News.

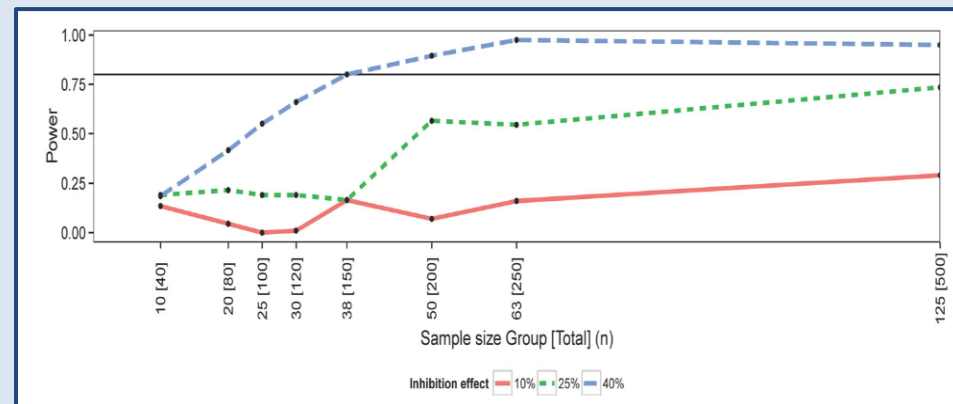
[2] Ludwig E, Bihorel S, Fiedler-Kelly J. Addendum Report No. COG008041/2016/ESLIPEDSADD. January 2017. Cognigen Corporation



Assessing anti-fungal azole induced inhibition of vincristine clearance in pediatric oncology patients

Key Question: What is the optimal study design to determine a clinically relevant drug-drug interaction of different azole anti-fungal drugs on vincristine pharmacokinetic in pediatric oncology patients

- **Rationale:** Co-administration of azole anti-fungals and vincristine anti-cancer therapy in pediatric oncology patients is associated with increased toxicity. A clinical study was planned to study the effect of azole-induced inhibition of CYP3A4. However, study designs were associated with a risk for drop-out and missing samples
- **Data** - Adult population PK model and pediatric growth curves were utilized.
- **Method:** Clinical trial simulations using mixed effect models & D-optimal design
- **Results:** Trial simulations with optimized PK sampling design, and systematic assessment of dropout and missing PK samples were comprehensively assessed. A study design with >38 patients per drug-condition could detect a clinically relevant effect of >40% inhibition of clearance



Conclusions: Clinical trial simulation and optimal design allowed identification of a feasible clinical study design that could detect clinically relevant effects of azoles on vincristine pharmacokinetics.



Dose reduction of bedaquiline needed to mitigate the drug-drug interaction with ritonavir-boosted lopinavir

Key Question: How can bedaquiline (BDQ) safely be co-administered with ritonavir-boosted lopinavir (LPV/r)?

Data

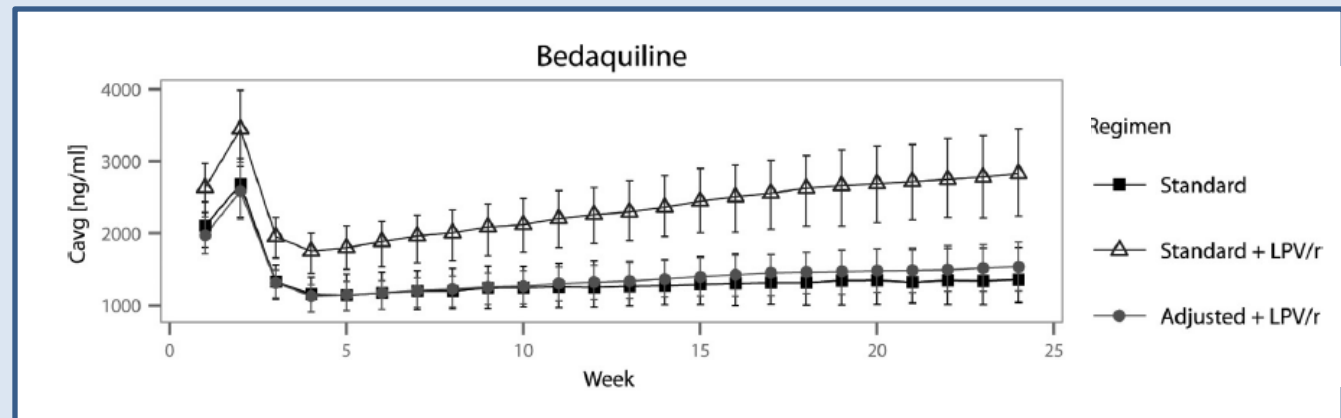
Concentrations of BDQ after single doses in a healthy volunteer drug-drug interaction study with LPV/r

Inference and Simulation

- Almost 3-fold BDQ increases in exposures during chronic treatment with LPV/r are expected, the safety of such exposures is unknown
- A 25% dose reduction in the loading phase and a 50% reduction in the continuation phase are predicted to normalize the exposure

Analysis Method

LPV/r's effect on BDQ pharmacokinetics was assessed by nonlinear mixed-effects modeling

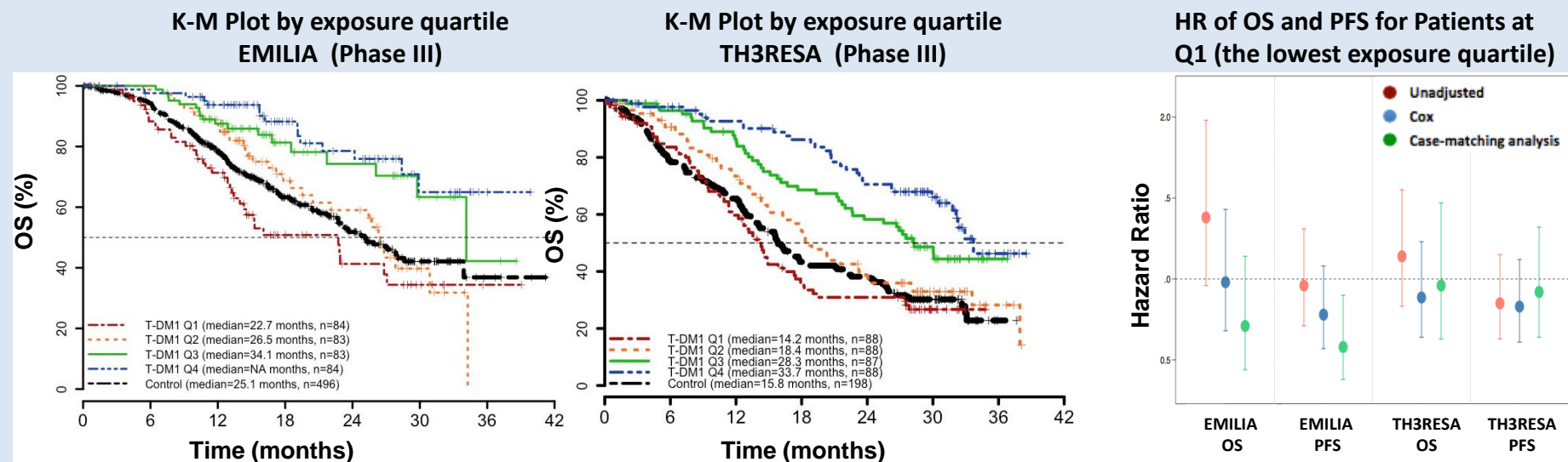


Conclusions: A dose reduction of bedaquiline is needed to mitigate the drug-drug interaction with ritonavir-boosted lopinavir. For drugs with pharmacokinetic properties preventing (close to) full PK curves from being captured, non-compartmental analysis under-predicts the impact of drug-drug interactions, and model-based analysis is necessary.



Dose Optimization of Kadcyra (T-DM1) in Patients with Therapeutic Use & Special Populations HER2-Positive Metastatic Breast Cancer

Key Question: Is there a need to optimize the dose in the patients who have lower T-DM1 exposure at approved dose (3.6 mg/kg q3w)?



Inference: K-M plots of OS and PFS (not shown) by model-predicted Cycle 1 C_{min} quartiles illustrate an apparent E-R relationship between exposure and survival outcomes. However, hazard ratios for OS and PFS for T-DM1-treated patients in the lowest exposure quartile (Q1) vs. active control were <1 after adjusting for baseline risk factors with Cox proportional-hazards models and case matching analysis.

Conclusions: Quantitative analysis that included risk factors helped us understand our data and address the potential need for a dose optimization study in patients with low exposure. The comprehensive ER analyses further demonstrated that the approved T-DM1 dose (3.6 mg/kg q3w) has a positive benefit-risk profile over active control, even for patients with low T-DM1 exposure, thus a dose optimization study in this patient subgroup may not be warranted.

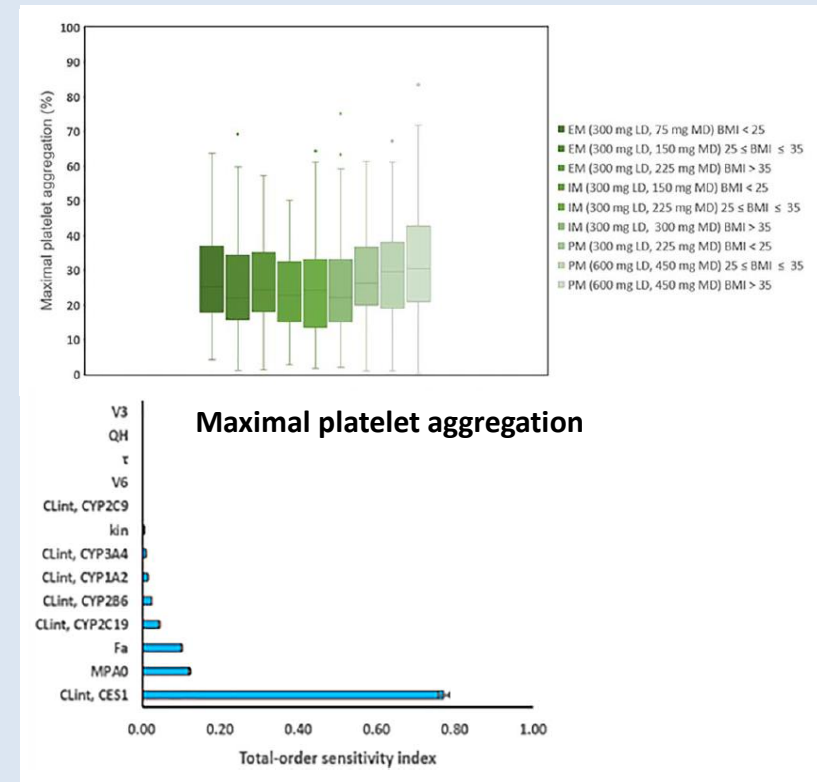
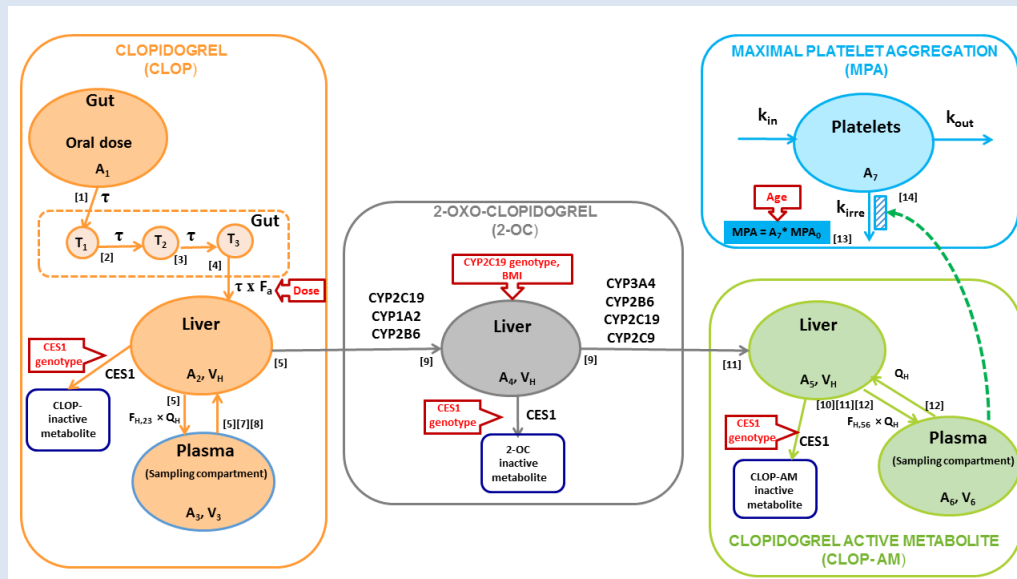


Identifying Clinically Relevant Sources of Variability: The Clopidogrel Challenge

Therapeutic Use & Special Populations

Key Question: What are the primary sources of the in part large interindividual variability in response to clopidogrel treatment and how do they impact dose selection in patient subgroups?

Background: CYP2C19 polymorphisms, age, obesity and DDIs have been identified as important factors impacting clopidogrel-mediated antiplatelet effects. Dose adjustment is recommended for CYP2C19 PMs (boxed warning from FDA).

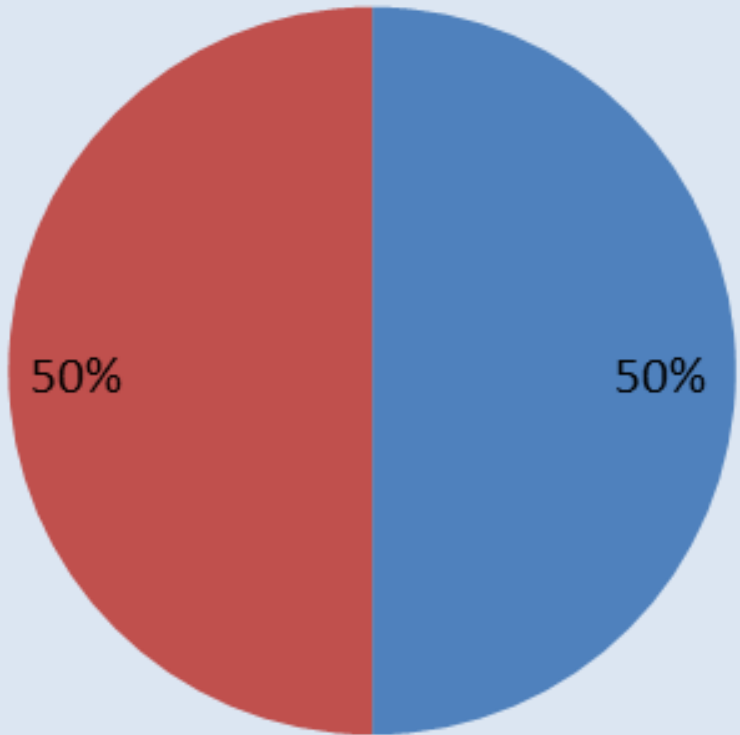


Conclusions: Higher maintenance doses are required for CYP2C19 IMs and PMs compared to EMs. A further dose increase may be needed in morbidly obese and super obese subjects. Results of our global sensitivity analysis suggest that interindividual differences in relative bioavailability (F_a), CES1 activity and baseline platelet reactivity (MPA_0) are other sources of clinically significant variability in response to clopidogrel treatment.



Key Application Area

Cost-effectiveness & Differentiation



Key Application Sub-areas

■ Go/no go decisions

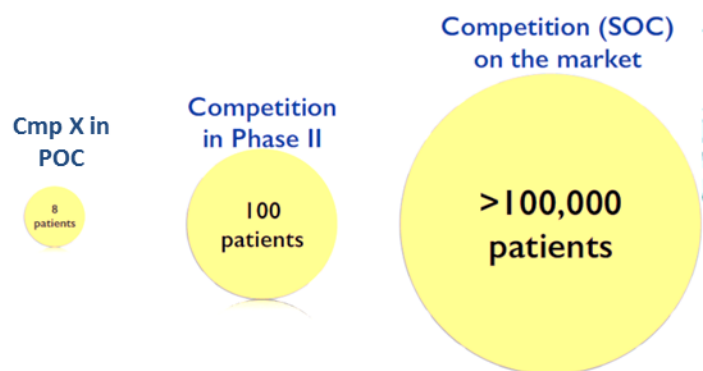
■ Pharmaco-economic assessment

Early Go/No Go based on differentiation potential compared to competitors and early patient data

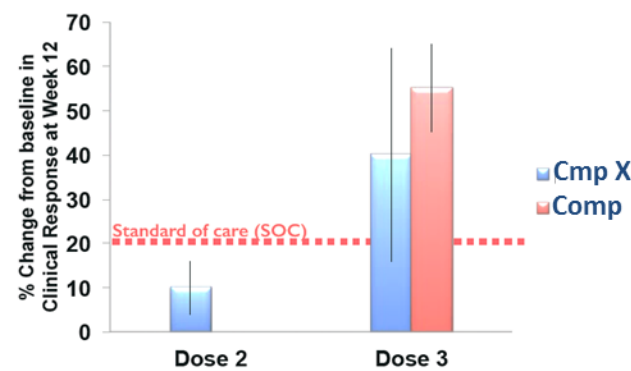
Cost-Effectiveness & Differentiation

Key Question: Does the compound have sufficient differential potential to SoC to support continuation of Ph1b POC study in patients?

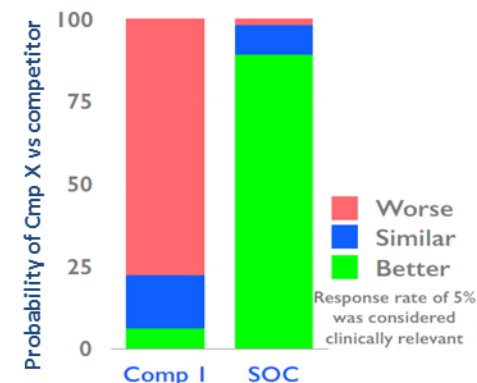
Little data to assess differentiation



Model-Based Meta Analysis



Differentiation Potential



Inference

- Probability of Cmp X being comparable to that of the competitor was low without changes in clinical strategy, despite it would offer improvement over current standard of care.

Conclusions

- Quantitative analysis enabled efficient decision making on a moderate effective drug despite “little” data. Based on the limited available options to revise the clinical strategy and the competitor substantially ahead in the development, the decision was made not to enroll more patients, and stop the program



Early Decision to Terminate Program Based on Projected Lack of Differentiation from Other Anti-Diabetic Agents

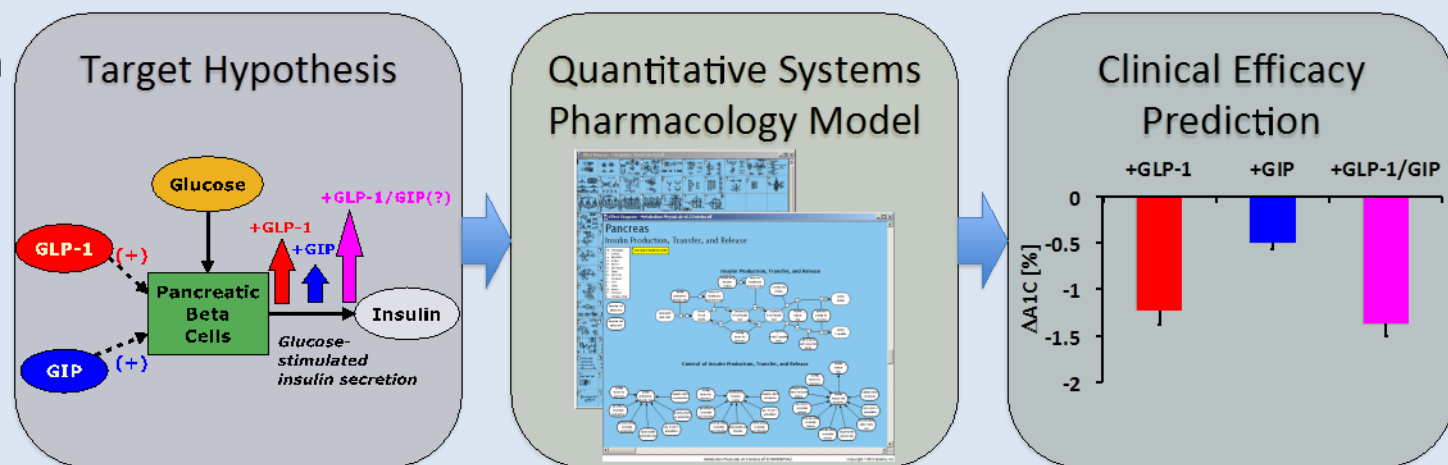
Cost-Effectiveness
& Differentiation

Key Question: Can a dual GLP-1 + GIP agonist sufficiently differentiate from existing GLP-1 agonists for the treatment of type 2 diabetes?

Data – Extensive literature on incretin biology and their effects on both healthy volunteers and patients with T2D.

Modeling Approach

Physiologically-based modeling of human metabolism using the Entelos Metabolism PhysioLab



Results - The effect of high-exposure GIP was predicted to be -0.4% A1C in diabetics without any GLP-1 therapy. This delta was reduced to less than -0.15% A1C with increasing concentration of GLP-1.

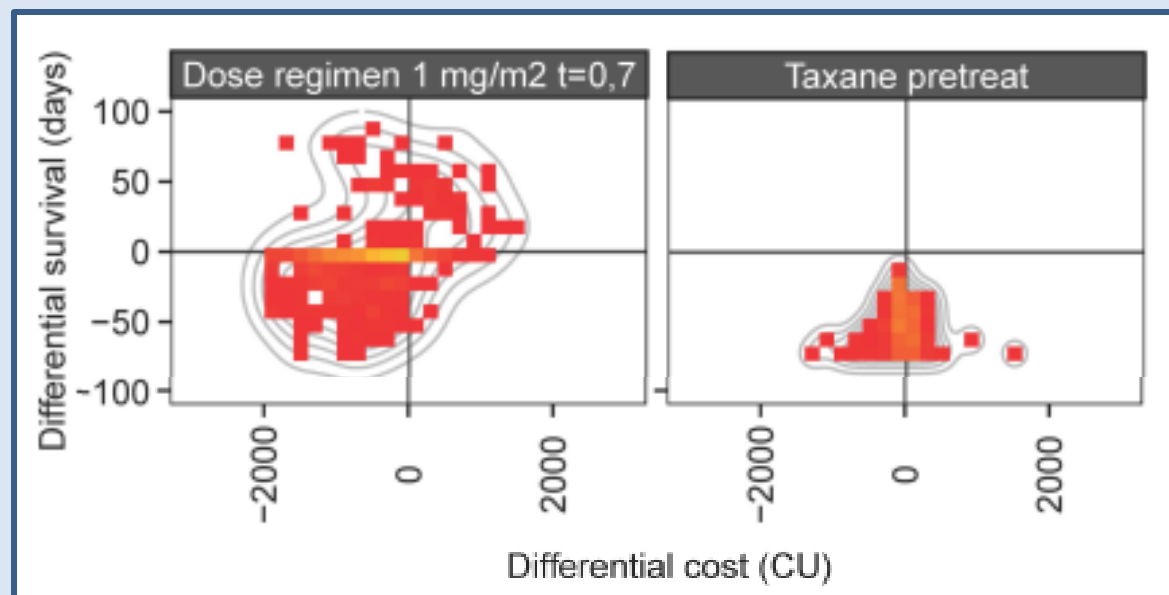
Inference - Some additional efficacy was possible through dual incretin action, but the added benefit was still clinically similar to existing incretin therapies

Conclusion: The model could not make a firm case for superiority of a dual-agonist. This analysis was a contributing piece to the project team's recommendation to cease development

Early prediction of cost-effectiveness of anti-cancer agents using a PKPD modeling approach

Key Question: What is the impact of dose regimens and trial designs, and different patient populations, on cost-effectiveness of anti-cancer agents?

- **Data** - Efficacy and toxicity models from multiple phase II and III trials involving the anti-cancer drug eribulin.
- **Method** - Integrative simulations of multiple mixed effect models for toxicity and efficacy biomarkers and clinical outcomes.
- **Result** - Differential clinical outcome and cost-effectiveness profiles were generated.



Conclusions: Dose regimens, trial designs, and differences in patient populations can significantly impact expected cost-effectiveness profiles. This study shows the value of PKPD modeling to generate early mechanism-based predictions of cost-effectiveness

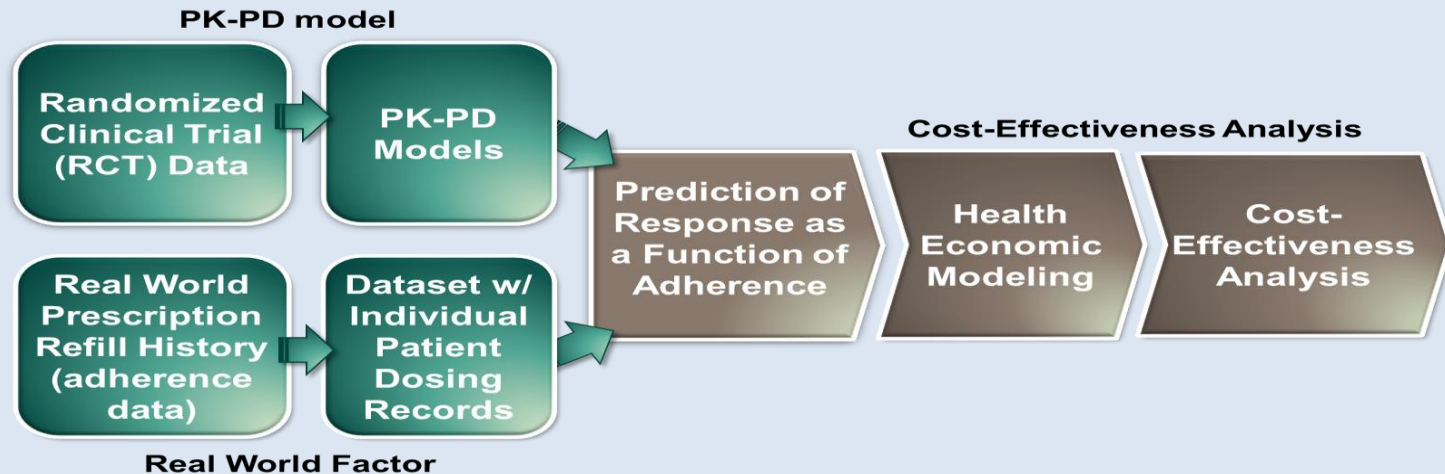


PK-PD and Health Economic Modeling to Inform Cost-Effectiveness of Improving Adherence in Real-world Setting

Cost-Effectiveness & Differentiation

Key Question: Would a hypothetical new drug/technology offering better adherence for a diabetes drug be more cost-effective compared to existing standard of care?

- Data & Model:** PK-PD model linking dose with HbA1c response was built using existing data for a once-daily diabetes drug. Real world data from a large prescription history dataset was integrated with the PK-PD model to quantify the impact of adherence on HbA1c response. These results were incorporated in a health economic model to project the long-term impact on health outcomes.



- Inference:** With the observed adherence rate for once-daily diabetes drug, hypothetical new drug providing better adherence was cost-effective (using € 25,000 per QALY gained as threshold) only for treating patients who were less than 80% compliant with the old drug

Conclusions: PK/PD models could provide otherwise not-yet available information as inputs for health economic models to allow meaningful cost-effectiveness evaluation of a new drug vs. an old drug during the development of a new drug

