March 31, 2017

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

Feedback & Questions

- Satyaprakash Nayak Satyaprakash.Nayak@pfizer.com
- Sandra Visser sandra.visser@merck.com

- 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.

Acknowledgements

- QP network leads
  - Anne Heatherington & Karthik Venkatakrishnan
- ASCPT
  - Lisa Williamson
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March 31, 2017

Case Study Compendium

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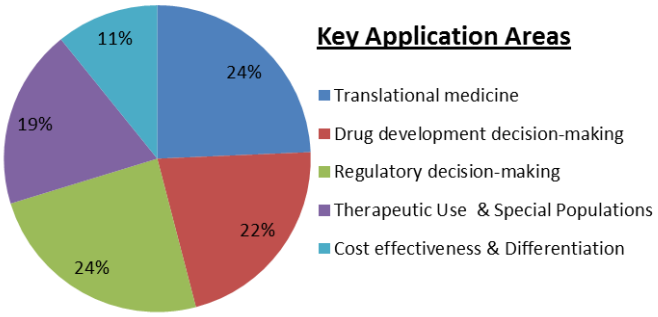

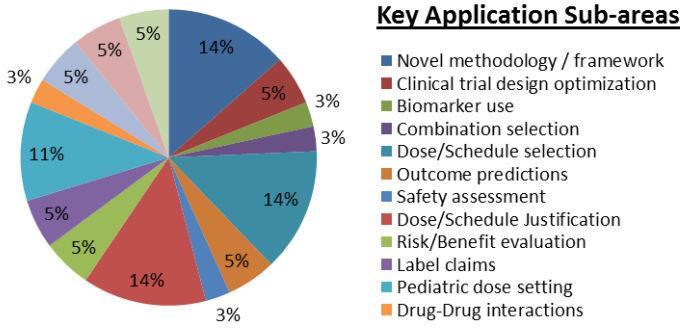

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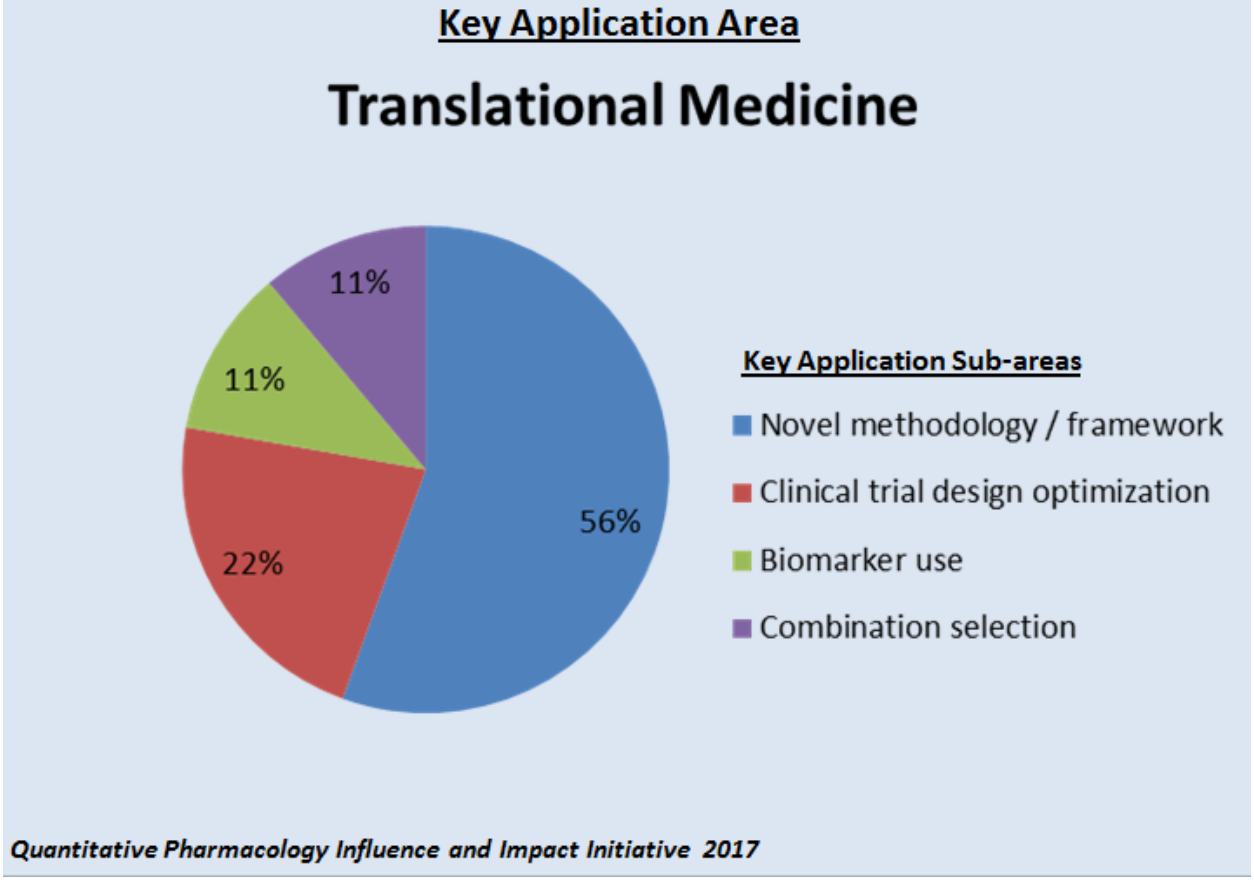


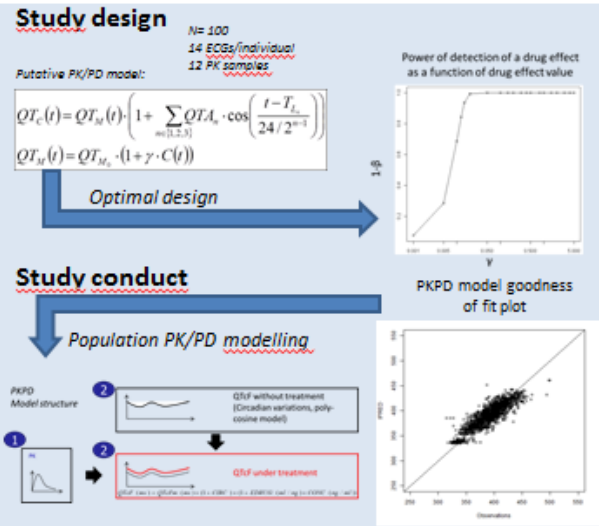
Translational Medicine, Case Study #1

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

Translational Medicine

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



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

PAGE 23 (2014) Abstr 3052 [www.page-meeting.org/?abstract=3052]

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How to assess cardiac safety in early oncology trials using optimal design and M&S approach
	Quantitative Pharmacology-informed conclusion	A framework for an accurate quantification of QTc prolongation with a feasible ECG recording design in oncology patients
	Application Area	Translational Medicine, Novel methodology / framework
Case study Details	Background / Introduction	In the specific context of oncology, QT studies are more difficult to perform. An accurate description of the PKPD relationship between drug concentration and corrected QT (QTc) may be performed by analyzing electrocardiogram (ECG) data collected in early clinical trials. However, the constraints of phase I studies in patients limit the flexibility of administration and measurement schedules.

	Data Availability	PK and ECG in a phase I study in patients
	Modeling / Analysis Method	Optimal design was performed in order to assess the power of detection of a significant drug effect, given an ECG monitoring design, and a PK sampling design. Then the PKPD analysis was performed.
	Results	A power of detection greater than 80% for a non-negligible effect (>10ms) of drug S on QTc was estimated. Then, when data was obtained the PKPD analysis was able to quantify concentration/effect relationship.
	Inference /Simulation / Extrapolation	Model outcome ultimately will have to be compared to concentration range obtained at the recommended dosing order to cover the variability of concentrations in clinical routine use.
	Conclusions	This framework allowed the assessment of the ability of the study design to inform on concentration-QTc relationship, and allowed the assessment of this relationship.
	References / Acknowledgements	Cardiac safety monitoring in early oncology trials using optimal design and M&S approach PAGE 23 (2014) Abstr 3052 [www.page-meeting.org/?abstract=3052]
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Safety & Tolerability
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium for this work, but potential for High (replace TQT study)

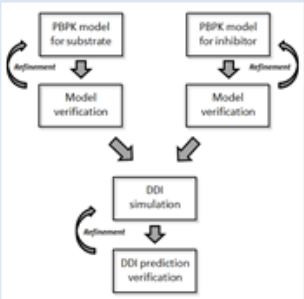
Translational Medicine, Case Study #2

PBPK prediction of renal transporter-mediated DDI

Translational Medicine

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 Ki 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.

Contactperson: marylore.chenel@servier.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can PBPK modeling be used to predict renal transporter-mediated DDI?
	Quantitative Pharmacology-informed conclusion	A reasonably good prediction of clinical DDI was obtained using the PBPK model, however more examples in this area will be required in order to conclude on a general level.
	Application Area	Translational Medicine, Novel methodology / framework
Case study Details	Background / Introduction	PBPK is an important approach for the prediction of DDI; however, it is currently mainly used for the prediction of metabolic DDI, and not transporter-mediated DDI. This example shows the prediction of organic anion transporter mediated renal DDI, and subsequent comparison with clinical DDI study results.
	Data	PBPK model input parameters for the Servier drug S 44121, ciprofloxacin,

	Availability	tenofovir and probenecid, and clinical DDI study results
	Modeling / Analysis Method	PBPK models created in Simcyp for S 44121, ciprofloxacin, tenofovir and probenecid. Simulations carried out, and compared to observed data (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 Ki value. The model correctly predicted that there would be no interaction between S 44121 and tenofovir or ciprofloxacin.
	Inference /Simulation / Extrapolation	The simulation showed that no DDI was expected between S 44121 and tenofovir or ciprofloxacin and 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 Cmax and IC50, 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.
	References / Acknowledgements	
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	PK
	MID3 Level	Compound
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	Medium

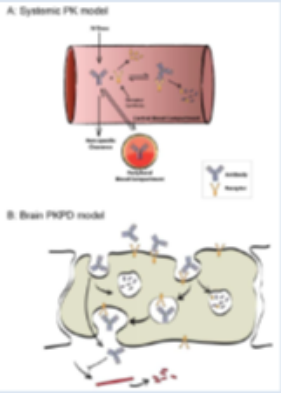
Translational Medicine, Case Study #3

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

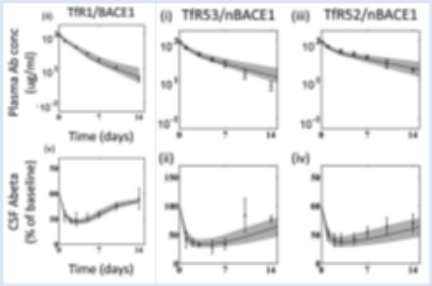
Translational Medicine

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?

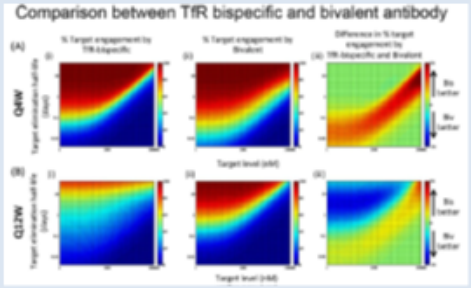
Model Structure



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.

Kanodia JS and Gadkar K et. al. Prospective Design of Anti-Transferrin Receptor Bispecific Antibodies for Optimal Delivery into the Human Brain. CPT:PSP (2016)

Contactperson: jitendra.kanodia@gmail.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	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?
	Quantitative Pharmacology-informed conclusion	The described modeling and simulation framework could predict the profile of expected human response for a specific antibody against a specific 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 the therapeutic bispecific antibodies
	Application Area	Translational medicine, Novel methodology / framework
Case study Details	Background / Introduction	Anti-transferrin receptor (TfR)-based bispecific antibodies have shown promise for boosting antibody uptake in the brain. Nevertheless, there are limited data on the molecular properties, including affinity required for successful development of TfR-based therapeutics. A complex non-monotonic relationship exists between affinity of the anti-TfR arm and brain uptake at therapeutically relevant doses. However, the quantitative nature of this relationship and its translatability to humans is heretofore unexplored. Therefore, we developed a mechanistic pharmacokinetic-pharmacodynamic (PK-PD) model for

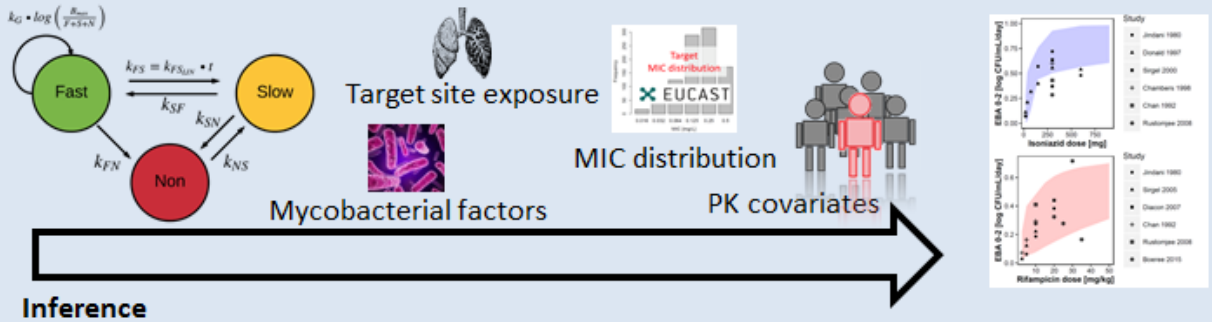
		bispecific anti-TfR/BACE1 antibodies that accounts for antibody-TfR interactions at the blood-brain barrier (BBB) as well as the pharmacodynamic (PD) effect of anti-BACE1 arm.
	Data Availability	Data is published in CPT:PSP Kanodia et. Al. 2016
	Modeling / Analysis Method	Differential equation based model built, simulated and optimized in MATLAB
	Results	In this work, we developed a mechanistic PK-PD model that accounts for target-mediated clearance of anti-TfR/BACE1 bispecific antibody in plasma and affinity-dependent uptake into the brain by explicitly accounting for antibody-TfR interactions in plasma as well as on the brain endothelium. The model was extended to translate PK-PD predictions from Cynomolgus monkey to human and thereby aid in design of a molecule for clinical development. The model was then further applied to explore the impact of a range of target parameters that also play a role in whether an anti-TfR bispecific platform provides any advantage over a standard anti-target bivalent antibody approach.
	Inference /Simulation / Extrapolation	*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 response for a specific antibody against a specific 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 the therapeutic bispecific antibodies
	References / Acknowledgements	*Kanodia JS and Gadkar K et. al.* Prospective Design of Anti-Transferrin Receptor Bispecific Antibodies for Optimal Delivery into the Human Brain. CPT:PSP (2016)
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Disovery
	MID3 Theme	Efficacy
	MID3 Level	Mechanism
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	Medium

Translational Medicine, Case Study #4

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

Translational Medicine

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



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

Authors: *S.G. Wicha, O. Clewe, C. Chen, L. Tanneau, R.J. Svensson, U.S.H. Simonsson. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.* ***References:*** *Wicha et al. ECCMID 2016; Clewe et al. JAC. 2016; Svensson et al. CPT:PSP 2016, Clewe et al. Eur J Clin Pharmacol 2015*

Contactperson: Ulrika.Simonsson@farmbio.uu.se

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How to optimally select clinical anti-tuberculosis drug combination regimens from pre-clinical studies using a translational pharmacometric approach?
	QP-informed conclusion	Innovative Phase IIa/b regimens and designs can be selected based on pre-clinical information in a quantitative and integrated approach.
	Application Area	Translational medicine; Clinical trial design optimization; Drug development decision-making
Case study Details	Background / Introduction	The evidence for the current treatment paradigms (drugs and doses) used in treatment of tuberculosis (TB) is weak and not based on pharmacokinetic-pharmacodynamic (PKPD) principles. The Multistate Tuberculosis Pharmacometric (MTP) model is a recently developed semi-mechanistic PKPD model describing the growth and drug effects on different bacterial sub-populations [1]. While the model was developed using *in vitro* data, it has been successfully applied to both mouse and clinical *in vivo* data [2], making it an appealing tool for use in TB drug development. In addition, a recent model-informed translational approach has been developed where the MTP model was used to predict clinical response of monotherapy based on pre-clinical (*in vitro*) TB exposure-response information [3]. A key challenge during drug development of anti-TB drugs is to predict the efficacy of drug combinations due to potential of PD interactions. Therefore, in addition to the MTP model, the general pharmacodynamic interaction (GPDI) model was recently developed which was shown to correctly predict PD interactions of more than two drugs and being superior to earlier proposed analysis methods [4]. A novel pharmacometric model-based framework for translational predictions of clinical efficacy of anti-TB drugs, both in monotherapy and in combination, using the MTP-GPDI model approach is proposed.

	Data Availability	The pharmacometric models used in this work were based on data from multiple sources. The disease model constituting the MTP model was based on *in vitro* natural bacterial growth data. Pre-clinical exposure-response model parameters were based on *in vitro* time-kill curves from monotherapy and combinations of multiple drugs. Drug PK was accounted for by using previously developed population PK models based on clinical data including human data on lung distribution into epithelial lining fluid [5] when applicable.
	Modeling / Analysis Method	The human population PK models were linked to the MTP model. For monotherapy, the exposure-response relationships were obtained using *in vitro* data and the MTP model only. For combinations of drugs, the GPDI model was linked to the PK-MTP models and *in vitro* data applied in order to account for PD interactions. In addition, the following translational factors were included in the clinical predictions and clinical trial simulations; (i) drug exposure in lung epithelial lining fluid, (ii) differences in mycobacterial susceptibility using published MIC distributions (e.g. from EUCAST) [6, 7], (iii) post-antibiotic effects, and (iv) inoculum effects (if applicable). The predicted clinical Phase II endpoint was "early bactericidal activity (EBA)".
	Results	The clinical exposure-response relationship in all historical observed EBA trials was correctly predicted for the two drugs isoniazid and rifampicin. The pharmacometric approach was able to correctly predict also the recently observed increased response after higher rifampicin doses (up to 35 mg/kg as compared with the clinically recommended dose of 10 mg/kg). Simulations also suggested that increasing the rifampicin dose even higher would result in an increased efficacy. Clinical EBA trials for isoniazid indicate a maximum achievable effect at doses marginally above the clinically recommended dose of 300 mg, which was also correctly predicted by the approach.
	Inference /Simulation / Extrapolation	The pharmacometric approach is closing the translational gap between preclinical and clinical development in TB drug development. The presented approach was used to simulate the efficacy after a currently unobserved clinical rifampicin dose of 50 mg/kg. The approach predicted an increased effect of rifampicin at doses higher than 35 mg/kg which supports clinical testing of a 50 mg/kg dose. In contrast, the approach predicted limited increase in effect of isoniazid at doses higher than in clinical use.
	Conclusions	The translational pharmacometric approach with the MTP model predicted successfully the entire known exposure-response curve of rifampicin and isoniazid EBA, which shows the potential of this methodology for TB drug development. As no PD parameters were re-estimated based on clinical data, the approach further demonstrated its potential for translation of pre-clinical TB information into a clinical setting. This allows support for dose selection of Phase IIa TB trials without the need of prior studies in TB patients. As the approach also includes a framework for studying PD interactions (GPDI model) it could inform the selection of combination regimens for Phase IIb TB trials.
	References / Acknowledgements	Authors: Sebastian G. Wicha, Oskar Clewe, Chunli Chen, Lénaïg Tanneau, Robin J. Svensson, Ulrika S.H. Simonsson. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. References: [1] O. Clewe et al., J Antimicrob Chemother. 2016;71(4): 964–74 [2] R. J. Svensson and U.S.H. Simonsson, CPT Pharmacometrics Syst Pharmacol. 2016;5(5):264-73 [3] S.G. Wicha et al. 26th European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, Netherlands, 9.-12. April 2016 [4] S. G. Wicha et al., PAGE meeting, Abstr 5946, 2016. [5] O. Clewe et al., Eur J Clin Pharmacol. 2015;71(3):313-9 [6] http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Rifampicin_rationale_1.0_2010_Oct.pdf; accessed on 30 Nov 2016 [7] T. Schön et al. J. Antimicrob Chemother, 2009;64: 786–93 Acknowledgements: The research was funded by the Swedish Research Council and the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement n°115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Discovery
	MID3 Theme	Clinical viability
	MID3 Level	Compound
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	High

Translational Medicine, Case Study #5

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

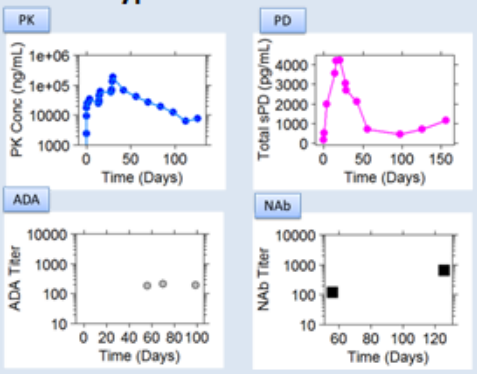
Translational Medicine

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

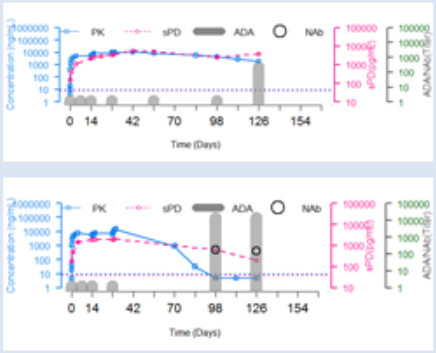
Background: Typically PK, PD, ADA and NAb data are summarized/plotted into different figures and often the interpretability is lost as one has to toggle through different plots

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

Acknowledgments: I. Bhattacharya, C. Banfield, C. Lepsy, K. Hung

Contactperson: Kosalaram.Goteti@pfizer.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Integrated visualization of PK, PD, ADA (Anti-Drug Antibodies) and Nab (Neutralizing Antibodies) Data of Biologics
	Quantitative Pharmacology-informed conclusion	A single plot of integrating all the information of a biologic to make informed and timely decision
	Application Area	Translational Medicine, Novel methodology / framework
Case study Details	Background / Introduction	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 to make a decision on the effect of one variable onto other
	Data Availability	PK, PD, ADA and Nab Data from Phase I study following a single or

		multiple dose with a typical monoclonal antibody
	Modeling / Analysis Method	Plotting was done using R
	Results	An integrated plot of PK, PD, ADA and NAb Data
	Inference /Simulation / Extrapolation	Helps in quick decision making during early drug development by understanding the effect of one variable onto other
	Conclusions	An integrated plot helps in enhanced visualization
	References / Acknowledgements	I. Bhattacharya, C. Banfield, C. Lepsy, K. Hung
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	PK
	MID3 Level	Compound
	MID3 Approach	n.a.
	Low / Medium / High impact	Low

Translational Medicine, Case Study #6

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

Translational Medicine

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)

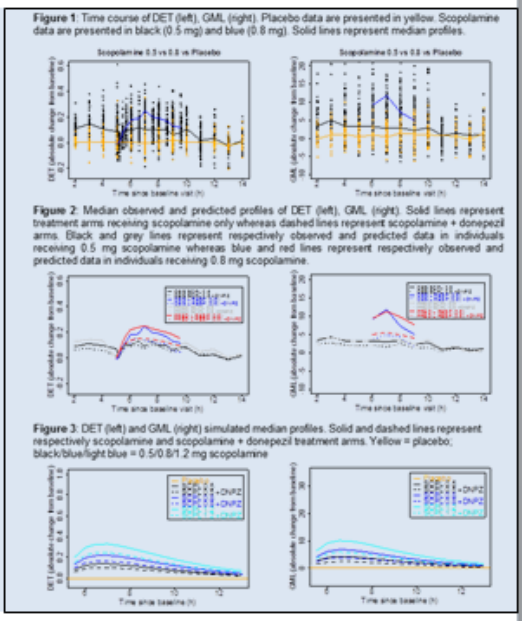


Figure 1: Time course of DET (left), GML (right). Placebo data are presented in yellow. Scopolamine data are presented in black (0.5 mg) and blue (0.8 mg). Solid lines represent median profiles.

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

Bellanti et al. J Pharmacokinet Pharmacodyn (2016) 43:S11–S122 M17

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can a meta-analysis help to optimize scopolamine challenge study design to evaluate NCEs targeting cognition impairment?
	Quantitative Pharmacology-informed conclusion	A higher scopolamine dose is required to obtain a more robust and consistent effect size in scopolamine challenge studies
	Application Area	Translational medicine; Clinical trial design optimization
Case study Details	Background / Introduction	The scopolamine cognitive impairment model has been widely used to ascertain pro-cognitive effects of development compounds. Drugs are assessed for their ability to reverse the scopolamine-induced impairment
	Data Availability	Five Phase I, placebo controlled studies pooled for the analysis of PK and PD data including Detection time (DET) and Groton Maze Learning (GML) endpoints from 159 healthy volunteers receiving 0.5 or 0.8 mg

		scopolamine and 10 mg donepezil
	Modeling / Analysis Method	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. The population analyses along with the simulations for the optimization of scopolamine challenge studies were performed using the NLME modeling approach with the software package NONMEM, v7.2.
	Results	DET and GML time-courses were well described by the models developed. 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.
	Inference /Simulation / Extrapolation	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.
	Conclusions	PKPD relationships of DET and GML were successfully characterized providing a framework that allows optimization of scopolamine challenge studies
	References / Acknowledgements	Francesco Bellanti[1], Claire H Li[2], Han Witjes[1], Thomas Kerbusch[1], Jason M Uslaner[3], Arie Struyk[4], Mark S Forman[4], Marissa F Dockendorf[2], and Sreeraj Macha[2];[1] Quantitative Solutions – A Certara Company, Oss, Netherlands; [2] Quantitative Pharmacology and Pharmacometrics, Merck & Co., Inc., Kenilworth, NJ, USA; [3] Pharmacology, Merck & Co., Inc., Kenilworth, NJ, USA; [4] Translational Pharmacology, Merck & Co., Inc., Kenilworth, NJ, USA
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Study design
	MID3 Level	Mechanism
	MID3 Approach	MBMA
	Low / Medium / High impact	Medium

Translational Medicine, Case Study #7

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

Translational Medicine

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

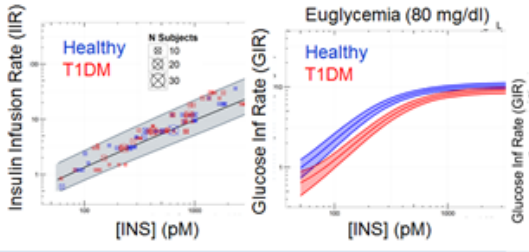
Popula-tion	Sources (Obs)		Data range (GLC -mg/dl, IIR -pmol/kg/min)			
	PK	PKPD	GLC ≤100	GLC >100	IIR ≤10	IIR >10
ND	15 (58)	14 (53)	37	21	36	22
T1DM	17 (71)	15 (56)	45	26	44	27

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.

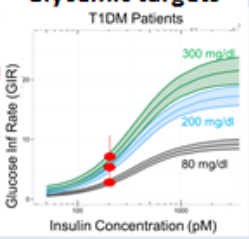
Results: Insulin CL saturable without PK differences HV/T1DM Insulin action is function of glycemic target. Insulin is less potent in T1DM compared to HV combined with reduced maximum.

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.

Fancourt et al. T12; Burroughs et al., W13. J Pharmacokinet Pharmacodyn (2015) 42:S11–S107.

Contactperson: craig_fancourt@merck.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How does the insulin PKPD relationship change as a function of glucose clamp targets in glycemic clamp studies to enable design of multi-glycemic clamp study
	Quantitative Pharmacology-informed conclusion	Design and comparator insulin dose setting for multi-glycemic clamp study to study novel insulin mechanisms
	Application Area	Translational Medicine, Clinical trial design optimization
Case study Details	Background / Introduction	The hyperinsulinemic glucose clamp is an experimental platform to measure insulin sensitivity by infusing exogenous insulin and glucose to measure insulin effect on whole-body glucose disposal rate (GDR) during homeostasis. We developed a pharmacokinetic (PK) - pharmacodynamic (PD) model of the hyperinsulinemic clamp that is physiologically plausible. The model was applied to hyperinsulinemic glucose clamp clinical data to quantitatively characterize differences in standard insulin PKPD in Type 1 diabetics (T1DM) compared to non-diabetics (ND) at various glycemic clamp levels.

	Data Availability	A literature search identified 21 clinical study publications examining glucose disposal rates (GDR) under different insulin infusion rates (IIR) and steady-state insulin ([INS]) and glucose ([GLC]) concentrations among T1DMs, with or without ND control groups (two seminal ND-only studies were included).
	Modeling / Analysis Method	The relationship between [INS] and IIR and GDR was described by a steady-state mechanistic PK-PD clamp model. The PK model consisted of saturable binding of insulin to the insulin receptor, expressed as target-mediated drug disposition, which at steady-state results in Michaelis-Menten saturable clearance, plus a non-specific linear first-order clearance. The PD model consisted of a non-insulin mediated glucose disposal, a non-linear and saturable insulin mediated glucose uptake, and a glucose auto-inhibition of glucose uptake.
	Results	Insulin clearance was saturable, resulting in total clearance declining with increasing insulin concentrations. No population differences in insulin PK were identified. A population difference was estimated for the maximum insulin-dependent glucose clearance and half-maximal insulin-mediated disposition. Compared to NDs, the [INS] required to maintain a given GDR was increased 1.5-fold among T1DMs, and the maximum GDR for a given fixed [GLC] target level was reduced 13% among T1DM subjects.
	Inference /Simulation / Extrapolation	Simulations based on these final models were performed in order to predict the GDR in T1DM and ND as a function of [INS] for different glucose clamp levels. These simulations are useful in identifying the range of experimental conditions at which T1DM subjects can be distinguished from ND, or which experimental conditions result in meaningful differences in GDR.
	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 can be used to design the comparator arm for (multi) glycemic clamp studies in both healthy subjects and T1DM patients.
	References / Acknowledgements	Fancourt C, Valiathan C, Tatosian D, Cho C, Visser SAG. Development of a Joint PKPD Model of the Hyperinsulinemic Glucose Clamp. J Pharmacokinet Pharmacodyn (2015) 42:S11–S107. T12 Burroughs E, Fancourt C, Dykstra K, Visser SAG. A Model-Based Meta-Analysis of Insulin PK-PD in Glucose Clamp Studies of Diabetes Mellitus Type 1 and Non-Diabetic Human Subjects. J Pharmacokinet Pharmacodyn (2015) 42:S11–S107. W13
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Study design
	MID3 Level	Mechanism
	MID3 Approach	MBMA
	Low / Medium / High impact	Medium

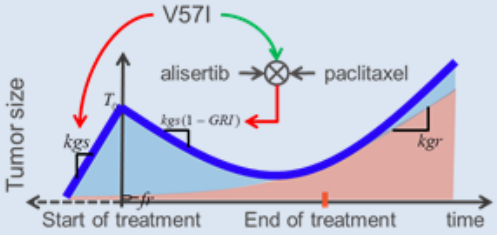
Translational Medicine, Case Study #8

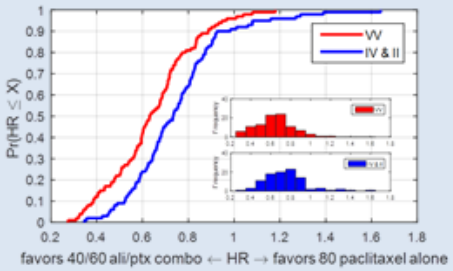
Dose-exposure-tumor kinetic modeling to determine strength of baseline biomarker as driver of antitumor effect

Translational medicine

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.

D. Bottino, K. Williams, H. Niu, A. Chakravarty, X. Zhou, J. Jung, M. Bargfrede, K. Venkatakrishan, ASCPT 2017

Contactperson: Dean.Bottino@Takeda.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What are the (baseline biomarker) drivers of antitumor effect, once dosing and exposure variability are accounted for?
	Quantitative Pharmacology-informed conclusion	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.
	Application Area	Translational medicine; Biomarker use
Case study Details	Background / Introduction	Prior statistical analyses showing a trend between alisertib target (AAK) SNP and progression free survival (PFS) outcome didn't consider dose and PK variability.
	Data Availability	PopPK parameters, SNP status, tumor size, and dosing in 107 ovarian patients

	Modeling / Analysis Method	Dose/PK/Tumor Kinetics modeling considering AAK SNP as a covariate
	Results	AAK SNP was a significant covariate in a few model parameters
	Inference /Simulation / Extrapolation	The SNP VV population was predicted to have a 10-20% better chance (than IV/II) of showing a PFS advantage of alisertib/paclitaxel over paclitaxel alone.
	Conclusions	We should enrich future alisertib ovarian cancer trials with VV patients.
	References / Acknowledgements	*D. Bottino, K. Williams, H. Niu, A. Chakravarty, X. Zhou, J. Jung, M. Bargfrede, K. Venkatakrishan, ASCPT 2017* (poster walk presentation)
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Efficacy
	MID3 Level	Disease
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	Medium

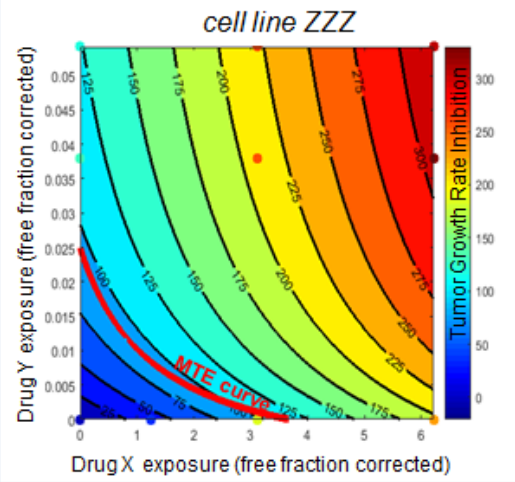
Translational Medicine, Case Study #9

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

Translational Medicine

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.

M Patel, E Kadakia, J Zhou, C Patel, K Venkatakrishnan, A Chakravarty, ***D Bottino****. ACOP 2016. J Pharmacokinet Pharmacodyn (2016) 43:S11-S122 T46*

Contactperson: Dean.Bottino@Takeda.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Given observed clinical toxicity and our preclinical understanding of exposure-response, what tolerable dose pair will give optimal antitumor effect?
	Quantitative Pharmacology-informed conclusion	This is a general methodology that can be applied to any early phase oncology combination when preclinical antitumor and clinical safety data are available.
	Application Area	Translational medicine, Combination selection
Case study Details	Background / Introduction	For the test case, we had a novel-novel combination in early development.
	Data Availability	Combination preclinical antitumor effect data. Clinical exposure & dose-limiting-toxicity (DLT) data.

	Modeling / Analysis Method	Logistic regression to determine 25% prob of DLT curve (MTE curve) Surface fitting mouse data to get free-fraction exposure → GRI relationship
	Results	Toxicity was slightly more synergistic than efficacy
	Inference /Simulation / Extrapolation	The optimum dose combination was predicted to be drug X given alone
	Conclusions	Once clinical tolerability is considered, monotherapy better than combo
	References / Acknowledgements	M Patel, E Kadakia, J Zhou, C Patel, K Venkatakrishnan, A Chakravarty, D Bottino. Identifying Optimal Dose Combinations of Anticancer Agents via Simultaneous Clinical Exposure-Toxicity and Preclinical Exposure-Efficacy Modeling. ACOP 2016. J Pharmacokinet Pharmacodyn (2016) 43:S11–S122 T46
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Clinical viability
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	High

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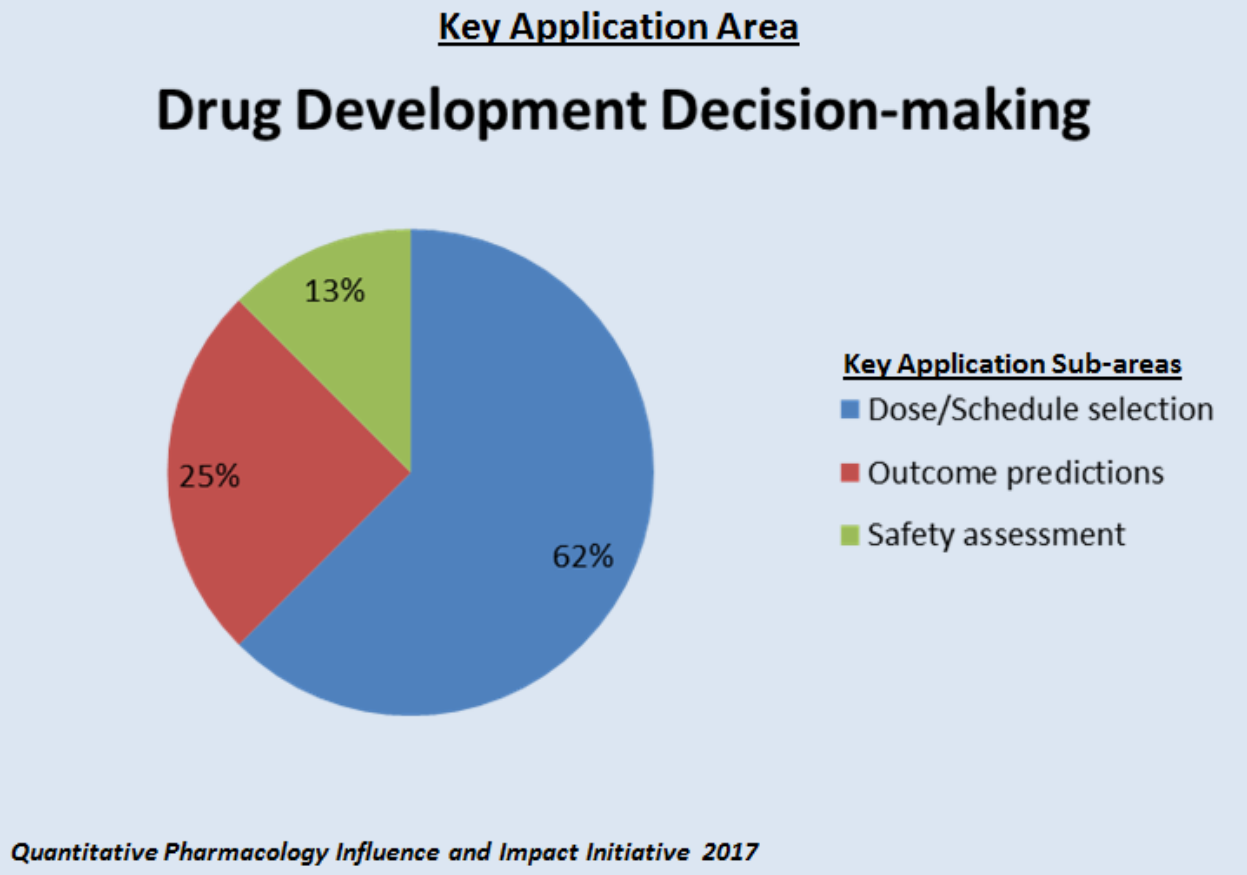


Drug Development Decision Making, Case Study #1

Model-based selection of the secukinumab dosing regimen in psoriasis

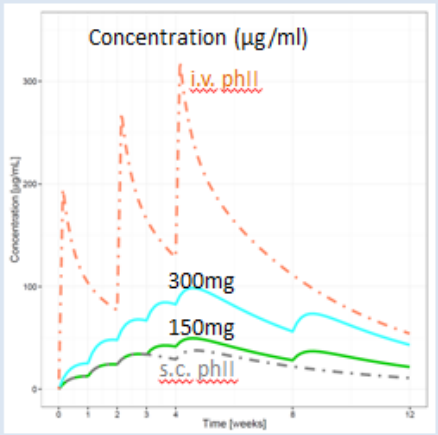
Drug Development Decision-making

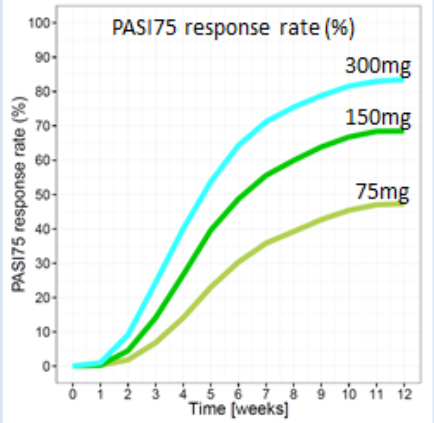
Key Question: What is the optimal dosing regimen to be used in phase 3?

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 be 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.

Contactperson: oliver.sander@novartis.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What is the optimal dosing regimen to be used in phase 3?
	Quantitative Pharmacology -informed conclusion	Model-based integration of phase I/II data allowed the selection of two dosing regimens for phase III which had not be tested previously. Phase III confirmed the positive benefit-risk for those regimens and the regimens were approved by regulatory authorities.
	Application Area	Drug development Decision-making, Dose/Schedule selection
Case study Details	Background / Introduction	In order to identify optimized dosing regimens for phase 3, this model-based analysis integrated data from several phase 2 studies that were collected under different conditions (i.e., different routes of administration, doses and dosing regimens, and study duration). The analysis was subsequently used to justify the selected regimens in the phase 3 study protocols, and at health authority meetings (end-of-phase-2 and advisory committee meeting after phase 3).
	Data Availability	Data from five phase I/II studies was integrated across different doses, regimens, and routes of administration

	Modeling / Analysis Method	Accompanying the phase 2 program, a population PKPD model was built in several iterations. When a new study read out, prior predictions of the read-out were checked against the new results and the model was subsequently refined and updated. A two-compartment PK model with zero-order (to account for IV administration) and first-order absorption (to account for SC administration) was fit to concentration data. Turnover models were fit to the continuous efficacy data (PASI score over time).
	Results	PK was described by a two compartment disposition model. PD was described by a turnover model with stimulatory effect on the decrease of disease activity (Kout), driven by a sigmoidal Emax model as a function of drug concentration. The PKPD model was considered predictive, as it captured the main trends across doses, dosing regimens and routes well.
	Inference /Simulation / Extrapolation	Based on this model, alternative dosing regimens were evaluated and two SC regimens were selected to move into phase 3: 150mg and 300mg given at weeks 0, 1, 2, 3, and 4 ("loading") followed by dosing every 4 weeks ("maintenance"). These two regimens were predicted to improve response over the subcutaneous regimens used in phase 2 and other treatments available on the market. As phase 2 studies had explored a wide exposure range – raning from low dose SC to high dose IV, the predictions can be seen as interpolations within the dose-exposure-response space spanned by regimens in phase 2.
	Conclusions	Through sequential integration of phase 2 data in model-based analyses, it was possible to recommend dosing regimens for phase 3 which had not been previously tested. The phase 3 studies confirmed the efficacy and safety of these new regimens, leading to regulatory approval of a product with optimized efficacy.
	References / Acknowledgements	[1] Sander O, Guettner A, Papavassilis C, Looby M. *Model-based development of the secukinumab dosing regimen for the treatment of moderate-to-severe chronic plaque psoriasis*. PAGE meeting 2016. [2] Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai TF, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C; ERASURE Study Group; FIXTURE Study Group. *Secukinumab in plaque psoriasis--results of two phase 3 trials.* N Engl J Med. (2014) 371(4):326-38.
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Efficacy
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	High (impact for sponsor:it allowed to progress with previously untested regimens into phase 3, leading to successful studies and approval)

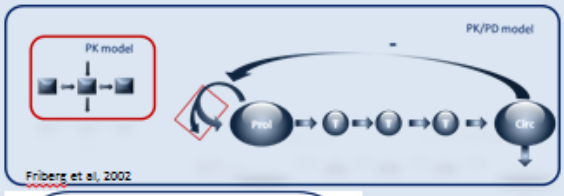
Drug Development Decision Making, Case Study #2

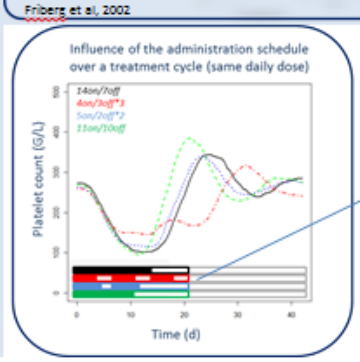
Determination of the optimal administration schedule using a PK/PD approach

Drug Development Decision-making

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





Solid boxes: treatment periods

Empty boxes: recovery periods

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.

Chalret du Rieu et al, Pharm Res, 2013 (DOI 10.1007/s11095-013-1089-1)

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How to predict an optimal administration schedule early in clinical development?
	Quantitative Pharmacology-informed conclusion	Early understanding of DLTs and PK determination allowed to build a PK/PD model, and model simulations allowed the determination of the optimal administration schedule
	Application Area	Drug development Decision-making, Dose/Schedule selection
Case study Details	Background / Introduction	During the first dose escalation trials in patients, several administration schedules were investigated, with few patients per schedule and dose and the observed dose limiting toxicity was consistently thrombocytopenia.
	Data Availability	PK and platelet counts from patients in first dose escalation trials
	Modeling /	Sequential PK & PK/PD analysis, using simulation-based model

	Analysis Method	qualification, then simulation of new administration schedules
	Results	A semi-mechanistic PK/PD model was able to describe all the available data, across administration schedules and doses.
	Inference /Simulation / Extrapolation	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	The final model, characterizing the dose-effect and the dose-toxicity relationships, provides a useful modeling tool for clinical drug development.
	References / Acknowledgements	Application of Hematological Toxicity Modeling in Clinical Development of Abexinostat (S-78454, PCI-24781), A New Histone Deacetylase Inhibitor . Chalret du Rieu et al, Pharm Res, 2013; DOI 10.1007/s11095-013-1089-1
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Safety & Tolerability
	MID3 Level	Compound
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	Medium

Drug Development Decision Making, Case Study #3

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

Drug Development Decision-making

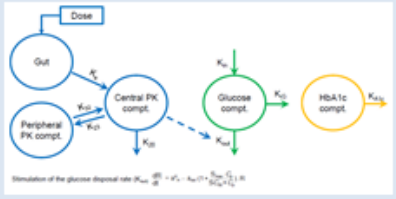
Key Question: What is the optimal dose range for a Ph2B study and does the compound have sufficient differential potential to DPPIVs?

Data:

SRD (PK) 16 | MRD (PK) 40 | POC (PK, FPG) 63

Modeling:

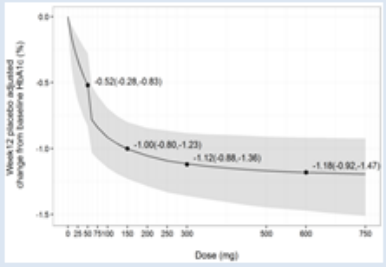
- An indirect response PK-FPG model was based on the pop PK model and FPG data from the clinical POC study.
- A published FPG-HbA1c relationship[1] was used to extrapolate MK-8666 FPG response to 12-week HbA1c



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 ≥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.

Vaddady et al., J Pharmacokinet Pharmacodyn (2016) 43:S11–S122 M46; [1] Naik et al., CPT:PSP 2013;2:e22

Contactperson: pavan.vaddady@merck.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What is the optimal dose range for a Ph2B study and does the compound have sufficient differential potential to DPPIVs
	Quantitative Pharmacology-informed conclusion	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.
	Application	Drug development Decision-making, Dose/Schedule selection
Case study Details	Background / Introduction	MK-8666 is a partial agonist for G protein-coupled receptor (GPR) 40, which was being developed to improve glycemic control in patients with type 2 diabetes mellitus. Pharmacokinetic (PK) and pharmacodynamic (PD) data from the clinical Phase 1 and Phase 1b studies were modeled to a) predict glycemic efficacy over 12 weeks from short-term glucodynamic data, b) guide dose selection for the Phase IIb study, and c) compare glycemic efficacy to new or existing oral antidiabetic agents.

	Data Availability	Single-ascending-dose (10 to 1000 mg) and once-daily multiple-ascending-dose (50 to 800 mg for 10 days) studies in healthy subjects and a once-daily multiple-dose (placebo, 50, 150, and 500 mg for 2 weeks) Phase 1b study in patients with T2DM.
	Modeling / Analysis Method	A population PK and PK-fasting plasma glucose (FPG) model was developed based on the data obtained. A previously published FPG-HbA1c relationship[1] was utilized to extrapolate MK-8666 FPG predictions to 12-week HbA1c response. Clinical trial simulations of plausible dose combinations were performed to evaluate the characterization of the overall dose-response curve. A previously developed comparator model on dipeptidyl peptidase IV (DPPIV) inhibitors were leveraged to identify a potential clinically efficacious dose with superior glycemic efficacy.
	Results	The PK of MK-8666 was characterized by a 2-compartment model with dose-dependent central volume of distribution and first-order absorption rate constant. An indirect response model with stimulation of glucose elimination well described the PK-FPG relationship. Based on simulations utilizing the PK-FPG model and FPG-HbA1c relationship, robust reductions in HbA1c at 12 weeks were feasible at 150 mg QD or higher, with smaller incremental benefits beyond 250- 300 mg QD. Doses around 500 mg and above were predicted to be at the Emax.
	Inference /Simulation / Extrapolation	Based on this analysis, doses of 50, 150, 300, and 600 mg QD were predicted to provide an adequate characterization of the overall dose-response curve. A potential clinically efficacious dose of 300 mg had the highest probability for a superior glycemic efficacy in comparison to DPPIV inhibitors.
	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 for a proposed Phase IIb study.
	References / Acknowledgements	Naik H, Lu J, Cao C, Pfister M, Vakilynejad M, Leifke E. Pharmacometric approaches to guide dose selection of the novel GPR40 agonist TAK-875 in subjects with Type 2 diabetes mellitus. CPT Pharmacometrics Syst Pharmacol. 2013;2:e22. Pavan Vaddady, Bharath Kumar, Alexander W. Krug, Elizabeth Migoya, Menghui Chen, Elizabeth Ommen, Daniel Tatosian, Prajakti Kothare. Pharmacokinetic and Pharmacodynamic Modeling of GPR40 Agonist MK-8666 Proof of Concept Data to Inform Clinical Decisions. American Conference on Pharmacometrics, Bellevue, WA, 2016.
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Clinical Viability
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD, MBMA
	impact	Medium

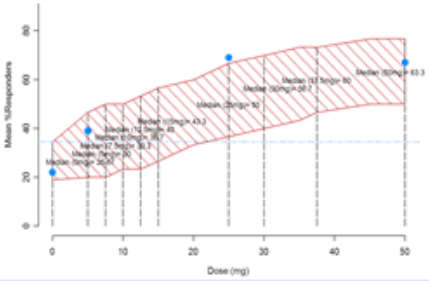
Drug Development Decision Making, Case Study #4

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

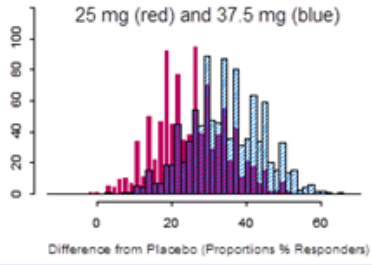
Drug Development Decision-making

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.

Al-Huniti et al CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 359–366

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What is the optimal dose of Naloxegol and best trial design for clinical phase III trial to confirm efficacy and safety?
	Quantitative Pharmacology-informed conclusion	Support Naloxegol clinical phase III dose selection and development decisions to design a robust phase III trial
	Application Area	Drug development Decision-making, Dose/Schedule selection
Case study Details	Background / Introduction	Naloxegol is a peripherally acting μ-opioid receptor antagonist for the treatment of opioid-induced constipation. Both 25- and 50-mg naloxegol was statistically significant over placebo in phase II study, but adverse events with increased frequency and severity were observed in the 50-mg cohort. The highest dose to be tested in Phase III studies became a critical decision at the stage.

	Data Availability	Phase 2 study
	Modeling / Analysis Method	Longitudinal dose-response and incidence of discontinuation (dropouts) to describe the weekly responder rate
	Results	Based on the simulated trials, the distribution of mean difference from placebo significantly overlaps between 25 mg and 37.5 mg dosing groups, suggesting that there would be little utility to using both the 25 mg and 37.5 mg dose levels in a single study.
	Inference /Simulation / Extrapolation	Inference
	Conclusions	25 mg Naloxegol was selected as the highest dose to be tested in Phase III studies.
	References / Acknowledgements	
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Efficacy
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium (Justify)

Drug Development Decision Making, Case Study #5

Application of Quantitative Systems Pharmacology Model to inform and speed early development of an SGLT2i

Drug Development Decision-making

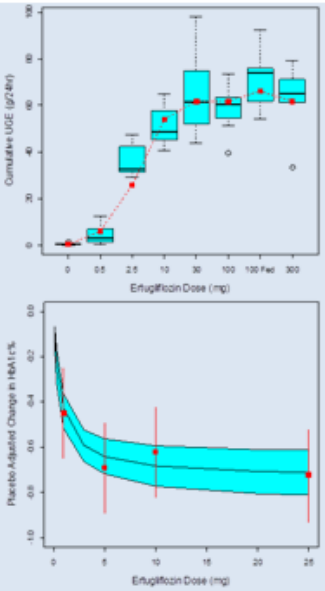
Key Question: Can we integrate target, physiology and disease in a comprehensive manner to predict efficacy in Type 2 Diabetes PoC Trial from healthy volunteers target engagement data?

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.

Milligan, P. A., et al. "Model-based drug development: a rational approach to efficiently accelerate drug development." CTP 93.6 (2013).

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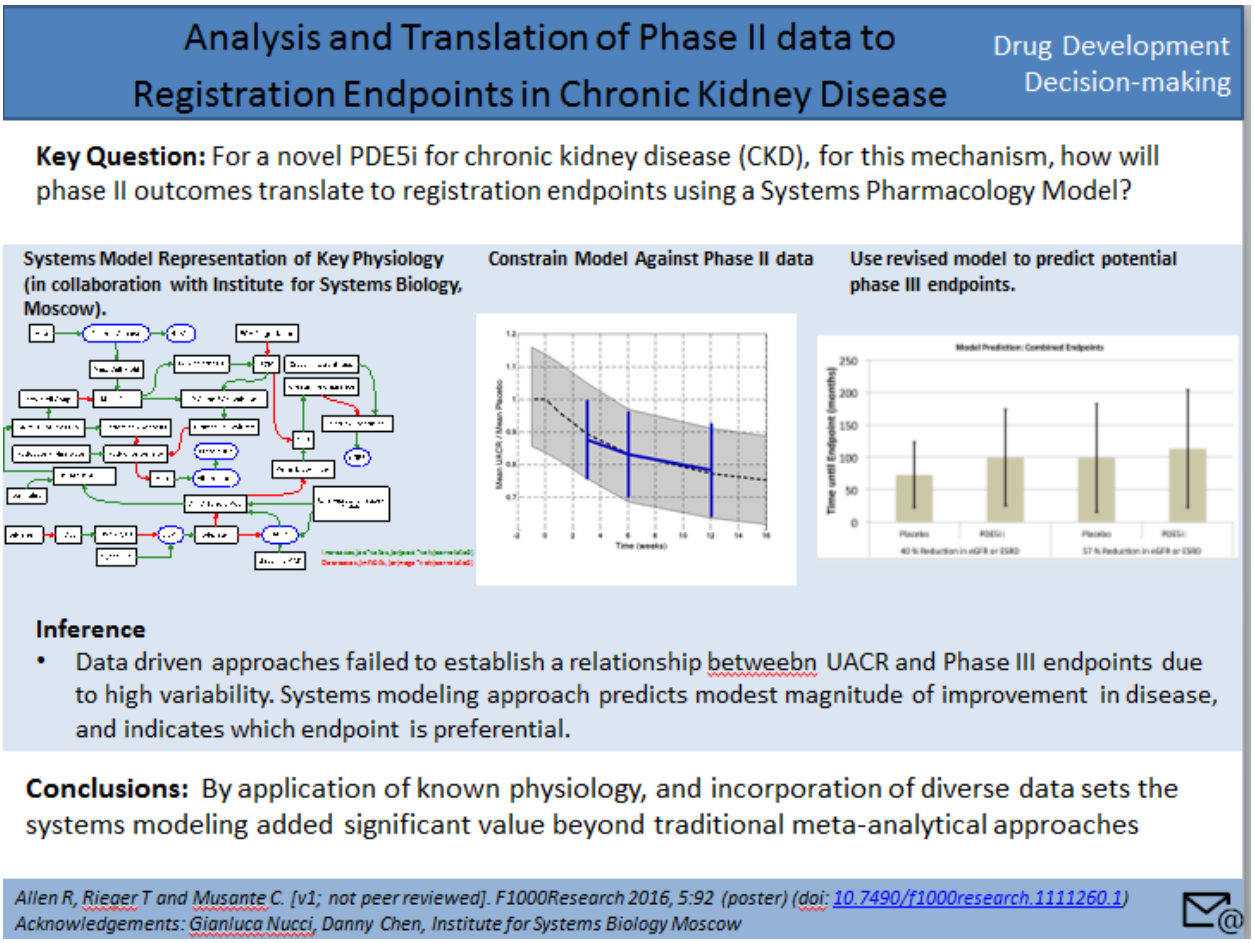
Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can doses for Ph2b be selected on the basis of PD measurements in PD?
	Quantitative Pharmacology-informed conclusion	Linkage from preclinical PK-UGE relationship through human UGE to human HbA1c and weight lowering using systems model, enabled confident nomination of a quality SGLT2i and accelerated its early clinical development
	Application Area	Development decision making, dose and schedule selection
Case study Details	Background / Introduction	During the discovery and development of PF-04971729 (ertugliflozin) Pfizer developed refined and extensively used modeling and simulation tools that have been applied to increase speed and enhance decision making of the program, spanning from simple, biologically based, PK/PD in the nonclinical phase of lead selection (to establish laboratory objectives for chemical optimization) to model based meta analyses (to assess comparative effectiveness within the class as well as against other antidiabetic agents) to the development and application of systems pharmacology models to increase the confidence in the dose selection and trial outcome.

	Data Availability	To inform the clinical development plan for ertugliflozin, we integrated the available data on the molecule, the physiologic understanding of the mechanism of action, and the published data on other SGLT2i compounds in a comprehensive model. This established a link between the mechanistic biomarker UGE in healthy subjects and improvements in glycemic control and body weight in longer-term studies in T2DM subjects. In order to do so we modeled SGLT2 inhibition in the Metabolism PhysioLab® platform.
	Modeling / Analysis Method	A physiologically based representation of competitive SGLT2 inhibition was added to the PhysioLab to account for the effect on glucose reabsorption in the proximal tubule which was tuned using publicly disclosed information on the PK and UGE profile for experimental SGLT2 inhibitors in both healthy and T2DM subjects and validated by comparing predictions of efficacy against a published 12 week trial.
	Results	Once the representation of the competitor SGLT2i was validated, a simultaneous representation of SGLT2 inhibition with ertugliflozin was implemented in the platform. Food intake was implemented as per clinical protocol. Modeled PK was introduced and drug potency for ertugliflozin was adjusted in real-time during the first in human study as PK and biomarker data with ertugliflozin became available to match UGE. The resultant model was used to simulate 12-week treatment with ertugliflozin to support dose selection for Phase 2 trial and the model predictions have been subsequently validated by comparison to the clinical data.
	Inference /Simulation / Extrapolation	The modeling approach undertaken to support dose selection for the Phase 2 study provided a quantitative link between UGE, the biomarker for the mechanism of action, and the long-term endpoints (HbA1C, body weight). Furthermore this allowed successful prediction of the changes in circulating insulin levels as well as providing grounds for simulating different dosing regimens and combination therapies.
	Conclusions	This information was used to successfully predict efficacy in T2DM patients from the observed first in human UGE data, and effectively project Phase 2 dose range out of a single dose escalation study in healthy subjects. This approach was one of the key drivers that allowed completion of the Phase 1 and 2 clinical exploration in 14.6 months
	References / Acknowledgements	Milligan, P. A., et al. "Model-based drug development: a rational approach to efficiently accelerate drug development." Clinical Pharmacology & Therapeutics 93.6 (2013).
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Efficacy,
	MID3 Level	Compound
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	Medium (Justify)

Drug Development Decision Making, Case Study #6



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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	For a novel treatment (PDE5 inhibition) for chronic kidney disease (CKD), how will phase II outcomes translate to registration endpoints?
	Quantitative Pharmacology-informed conclusion	Predicted Phase III response, and biomarker to endpoint relationship for mechanism/agent in question.
	Application Area	Drug Development Decision-making, Outcome predictions
Case study Details	Background / Introduction	Chronic Kidney Disease (CKD) is a significant unmet medical need. At least one reason for this is the difficult drug-development process for this disease. This is in part because of a lack of a reliable quantitative relationship between typical phase II endpoints (urinary albumin to creatinine ratio) and registrable endpoints (for example, time to end stage renal disease).
	Data	Summary data from a phase II trial a PDE5 inhibitor, literature data on the

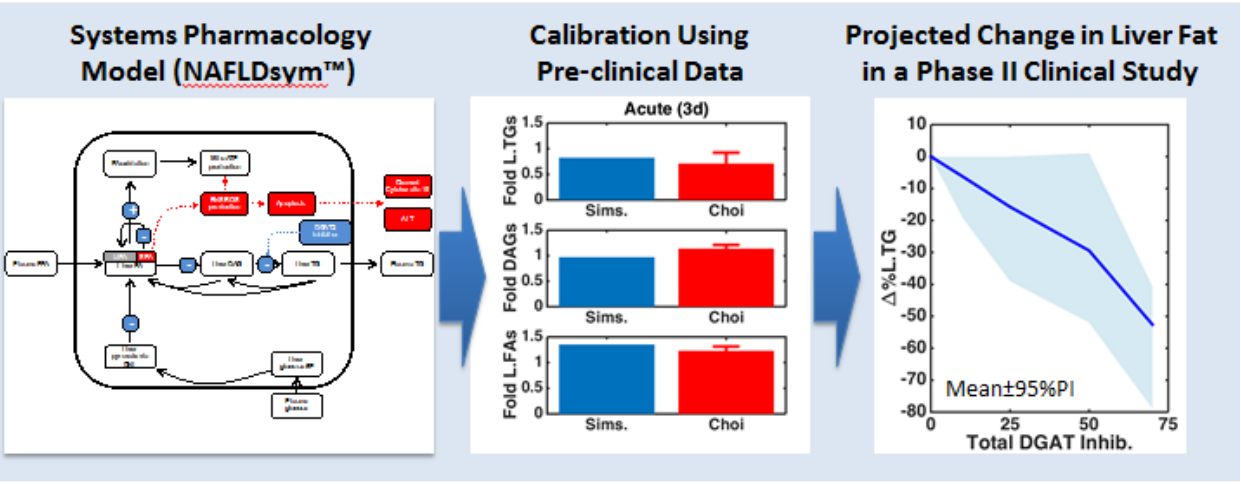
	Availability	effect of sildenafil on key physiology (for example blood pressure), pre-clinical data
	Modeling / Analysis Method	Systems model of CKD (built in collaboration with the Institute for Systems Biology Moscow) with key physiological processes represented including hypotheses for disease progression.
	Results	The model quantified both the estimate change in eGFR for given phase III trial lengths, and the uncertainty around that prediction by generation and analysis of a virtual population
	Inference /Simulation / Extrapolation	The analysis indicated that a combined endpoint of time to 40% reduction or ESRD would be preferential than time to 57% reduction in eGFR or ESRD.
	Conclusions	Quantitative analysis using a systems pharmacology model provided insight and key information to support decisions relating to phase II to III transition and design. In particular, assessments of efficacy and efficient trial design were addressed with the model, that could not have been established using data-driven approaches.
	References / Acknowledgements	Allen R, Rieger T and Musante C. Efficient generation of virtual populations of CKD patients and applications in quantitative systems pharmacology [v1; not peer reviewed]. F1000Research 2016, 5:92 (poster) (doi: 10.7490/f1000research.1111260.1) Acknowledgements: Gianluca Nucci, Danny Chen, Institute for Systems Biology Moscow
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Clinical Viability
	MID3 Level	Disease
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	High (Replace)

Drug Development Decision Making, Case Study #7

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)?



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).

http://www.dilisymservices.com; Choi et al. JBC. 2007; Acknowledgements: Cynthia Musante, Richard Allen, Jeffery Pfefferkorn, Arthur Bergman, Greg Tesz, Russell Miller, Jeff Chabot, Bob Dullea, Kendra Bence (Pfizer)

Contactperson: Cynthia.J.Musante@pfizer.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	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)?
	Quantitative Pharmacology-informed conclusion	DGAT inhibition has the potential to achieve significant reductions in liver fat, with a high enough inhibition. Model predicted significant variability in response to therapy.
	Application Area	Drug Development Decision-making, Outcome predictions
Case study Details	Background / Introduction	Non-alcoholic fatty liver disease (NAFLD) is a condition that may affect as many as 20-30% of Americans. The pathophysiology is associated with the accumulation of lipids in hepatocytes. Despite the disease's importance to the health of the population, there are no currently approved pharmacotherapies. One of the difficulties for conducting drug discovery in NAFLD is confirmation of reduction of L.TGs requires a liver biopsy, which

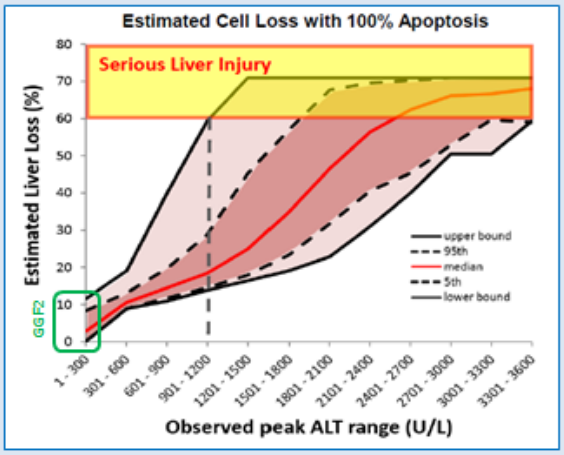
		can be both uncomfortable and possibly dangerous for patients. In order to bridge the gap between early (plasma) biomarkers and Phase IIb (biopsy endpoint), a systems model (NAFLDsym™) was calibrated for a novel treatment for NAFLD, inhibition of diacylglycerol acyl-transferase. Initially, pre-clinical experiments were used for the calibration (Choi et al. 2007). The simulations were then conducted to simulate 12-weeks of therapy in a cohort of simulated NAFLD patients.
	Data Availability	Pre-clinical data in various rodent models. Limited Phase I data for compound (e.g., PK, some plasma biomarkers).
	Modeling / Analysis Method	Modeling and Simulation
	Results	>25% 24-hr mean reduction in *total* DGAT activity was required to achieve clinically significant reductions in the mean of the simulations.
	Inference /Simulation / Extrapolation	DGAT inhibition does have the potential to extensively lower liver fat, but it may require a very high level of inhibition if just inhibiting one of the isoforms of the enzyme. Where the fatty acid flux goes in the hepatocytes with the inhibitor should also be investigated to ensure the therapy is not causing additional oxidative stress on hepatocytes.
	Conclusions	The developed systems model requires further validation, but is a reasonable starting representation of a NAFLD liver and can potentially be used to inform future clinical study design or target selection for NAFLD treatments.
	References / Acknowledgements	www.dilisymservices.com ; Choi et al. JBC. 2007;Acknowledgements: Cynthia Musante, Richard Allen, Jeffery Pfefferkorn, Arthur Bergman, Greg Tesz, Russell Miller, Jeff Chabot, Bob Dullea, Kendra Bence (Pfizer)
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Clinical Viability
	MID3 Level	Disease
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	Medium

Drug Development Decision Making, Case Study #8

Assessment of liver safety risk in Phase 1 GGF2 clinical trials

Drug Development Decision-making

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

Lenihan et al. J Am Coll Cardiol Basic Trans Science. 2016; Howell et al. CPT Pharmacomet. Syst. Pharmacol. 2014: 3, e98.

Contactperson: dlongo@DILIsym.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can mechanistic serum biomarkers and mathematical modeling determine the extent of hepatocyte loss and resultant impact on serum bilirubin in two subjects who met Hy's Law Criteria in clinical trials of GGF2?
	Quantitative Pharmacology-informed conclusion	Mechanistic biomarkers and mathematical modeling determined the maximum hepatocyte loss experienced by the two subjects would not cause a loss of global liver function sufficient to account for a significant rise in serum bilirubin. Hence, these two subjects should not be considered typical Hy's Law Cases.
	Application Area	Drug Development Decision-making, Safety assessment
Case study Details	Background / Introduction	GGF2 is an investigational drug for the treatment of heart failure. During Phase 1 clinical trials, concomitant, transient elevations in serum aminotransferases (ALT/AST) and bilirubin meeting Hy's Law criteria were observed in two treated subjects, although GGF2 has no direct toxic effect on human hepatocytes in culture. Resolution occurred within 2 weeks and with no further LFT

		abnormalities over the following 1-3 years.
	Data Availability	Serial serum samples were assayed for miR122, full length keratin-18 (FL-K18), caspase-cleaved K18 (ck18), and traditional liver chemistries.
	Modeling / Analysis Method	DILIsym® software, a mechanistic, mathematical model of drug-induced liver injury, was used to interpret the biomarker data. DILIsym® incorporates the release and clearance kinetics of traditional and novel biomarkers which are used as the outputs in liver toxicity prediction. Here, liver enzyme profiles were used as inputs to back-estimate the level of hepatocyte loss through apoptosis or necrosis.
	Results	miR122 values were elevated and consistent with liver origin of the ALT and AST elevations. The ck18/FLK18 ratio supported apoptosis as the major mode of GGF2-induced hepatocyte death. DILIsym® estimated that the maximum loss of hepatocytes in the two "Hy's Law" subjects was less than 13%, and that this amount of hepatocyte loss would not cause a significant rise in serum bilirubin. DILIsym® suggested that factors other than hepatocyte death underlie the rise in serum bilirubin in GGF2-treated subjects.
	Inference /Simulation / Extrapolation	With respect to liver function, the estimated level of cell loss (<13%) in GGF2-treated subjects would likely be practically undetectable and clinically benign. These results can be viewed in light of well-characterized compounds also known to routinely cause asymptomatic liver enzyme elevations. For example, the heparins, which do not cause clinically significant liver injury when taken as directed, were predicted to have hepatocyte loss <16% in healthy volunteers with ALT increases. The amount of hepatocyte loss predicted in GGF2 phase I subjects by DILIsym® was similar to the loss predicted for heparins.
	Conclusions	Traditional and novel biomarker analyses together with DILIsym® simulation results suggest that the two 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.
	References / Acknowledgements	Lenihan, D.J. et al. J Am Coll Cardiol Basic Trans Science. 2016: 1(7): 576-86. Howell, B. A. et al. CPT Pharmacomet. Syst. Pharmacol. 2014: 3, e98.
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug development
	MID3 Theme	Safety & tolerability
	MID3 Level	Compound
	MID3 Approach	Systems pharmacology and PBPK
	Low / Medium / High impact	Medium

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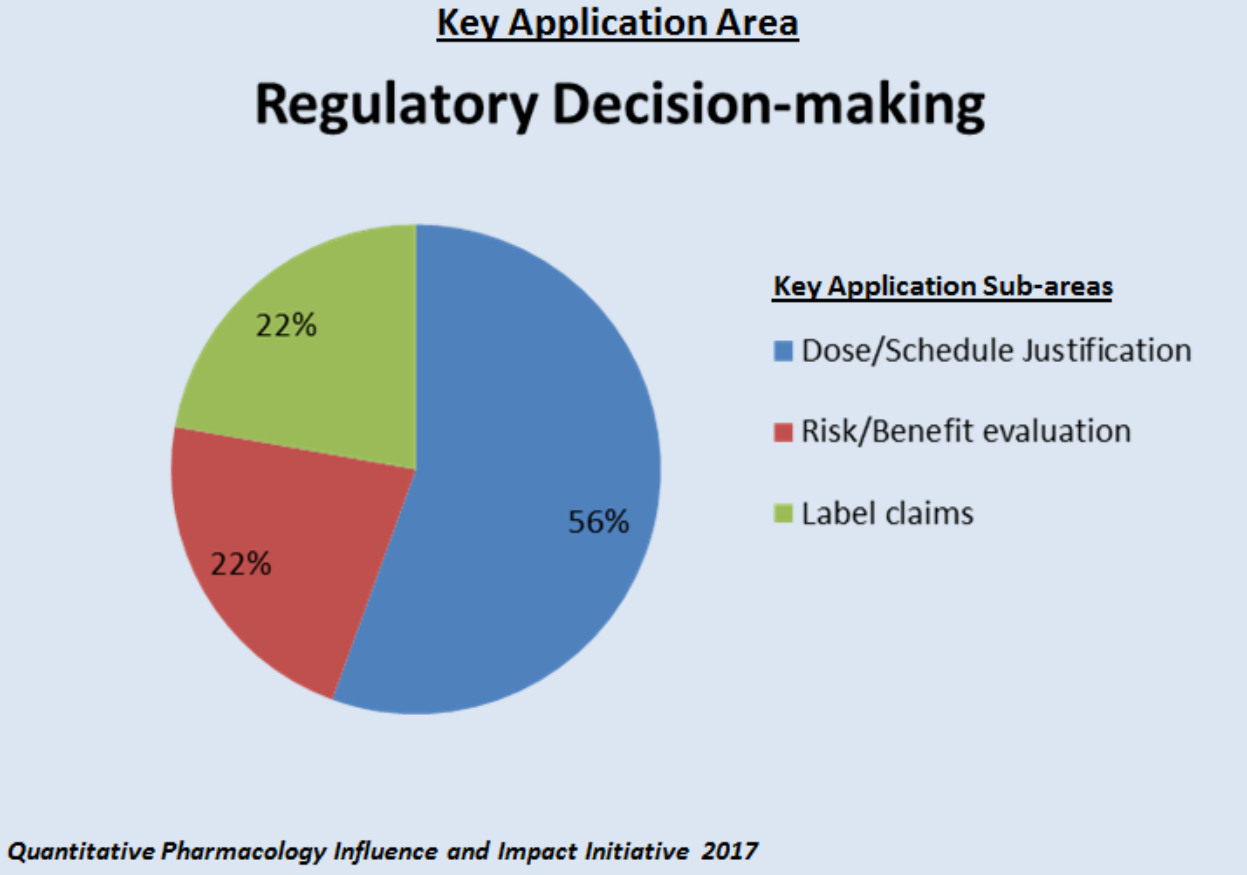


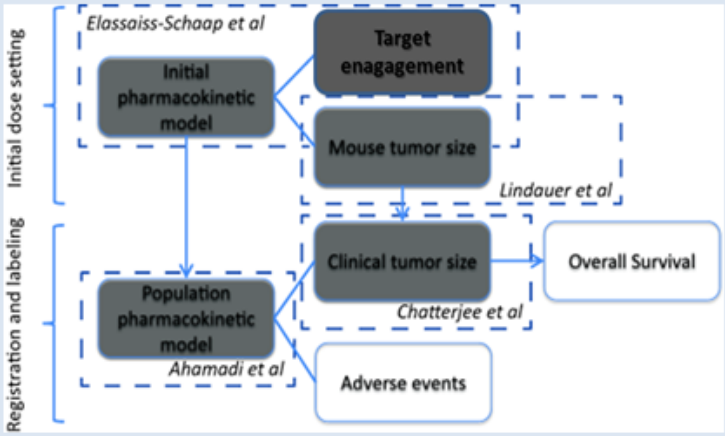
Regulatory Decision Making, Case Study #1

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

Regulatory Decision-making

- **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

CPT-PSP 2017: de Greef, R. et al., Pembrolizumab: Role of Modeling and Simulation in Bringing a Novel Immunotherapy to Patients With Melanoma. 6(1):5-7; Lindauer et al, 6(1):11-20; Elassaiss-Schaap et al., 6(1):21-28; Chatterjee et al., 6(1):29-39; Ahamadi et al., 6(1):49-57

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What is the optimal dose of Pembrolizumab?
	Quantitative Pharmacology-informed conclusion	For pembrolizumab, M&S drove the selection a efficacious dose of 2 mg/kg << maximum administered dose of 10 mg/kg
	Application Area	Regulatory Decision making, Dose/Schedule justification
Case study Details	Background / Introduction	Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks interaction with its ligands, PD-L1 and PD-L2. This binding results in the activation of T-cell–mediated immune responses against tumor cells.
	Data Availability	Preclinical and early clinical PK, and tumor-size

	Modeling / Analysis Method	PBPK, PK and tumor-size modeling
	Results	-Semi-mechanistic translational PBPK model suggested that the lowest dose regimen of pembrolizumab achieving a maximal response would be 2 mg/kg Q3W. -Tumor size measurements were adequately described by a model structure that captured continuous tumor size with a combination of growth and regression terms, as well as a fraction of tumor responsive to therapy. The model indicated that exposure to the drug was not a significant predictor of tumor size response over 2 to 10 mg/kg Q3W demonstrating that the dose of 2 mg/kg Q3W is at the plateau of maximal response.
	Inference /Simulation / Extrapolation	Modeling and simulations demonstrated flat dose/exposure-response over 2-10 mg/kg
	Conclusions	2 mg/kg is the efficacious dose of pembrolizumab.
	References / Acknowledgements	A Lindauer, CR Valiathan, K Mehta, V Sriram, R de Greef, J Elassaiss-Schaap, DP de Alwis; CPT Pharmacometrics Syst. Pharmacol. 2017; J Elassaiss-Schaap, S Rossenu, A Lindauer, SP Kang, R de Greef, JR Sachs, DP de Alwis; CPT Pharmacometrics Syst. Pharmacol. 2017; MS Chatterjee, J Elassaiss-Schaap, A Lindauer, DC Turner, A Sostelly, T Freshwater, K Mayawala, M Ahamadi, JA Stone, R de Greef, AG Kondic, DP de Alwis; CPT Pharmacometrics Syst. Pharmacol. 2017
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Efficacy
	MID3 Level	Compound
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	High

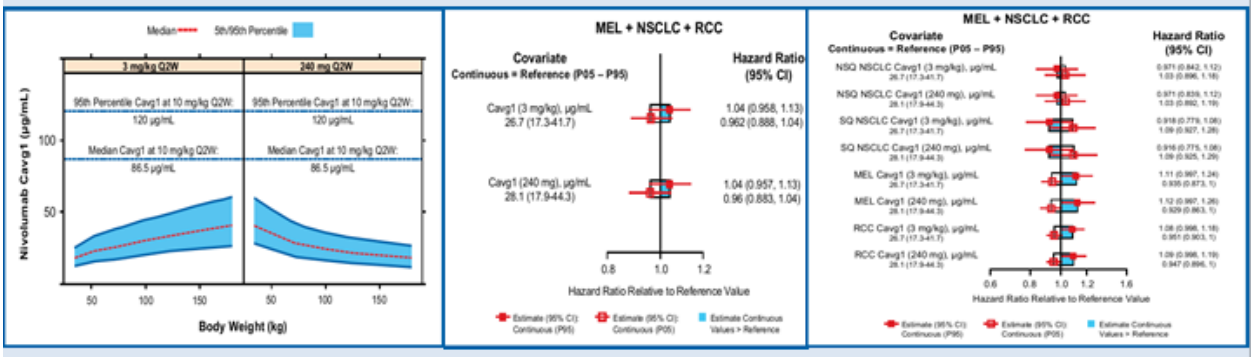
Regulatory Decision Making, Case Study #2

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.

Zhao X, Suryawanshi S, Hruska M, Feng Y, Wang X, Shen J, McHenry B, Waxman I, Achanta A, Bello A, Roy A, Agrawal S. 2016 European Society of Medical Oncology. Annals of Oncology (2016) 27 (6): 359-378

Contactperson: agrawal.scientist@gmail.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can quantitative clinical pharmacology approaches be used to assess benefit-risk profile and switch body weight based dosing (3 mg/kg Q2W) to flat dose (240 mg Q2W) of nivolumab?
	Quantitative Pharmacology-informed conclusion	Benefit-risk profile (as evaluated by pharmacokinetics, risk of experiencing adverse event and hazard for death) of flat dose of nivolumab 240 mg Q2W relative to 3 mg/kg Q2W was similar, and was the basis for approval of modified dose without clinical data.
	Application Area	Regulatory decision-making, Dose/Schedule justification
Case study Details	Background / Introduction	Nivolumab 3 mg/kg Q2W has shown benefit versus the standard of care in melanoma, NSCLC, and RCC. However, flat dosing may provide a consistent dose across body weights (BW) and is expected to shorten preparation time and improve ease of administration. With knowledge of nivolumab safety, efficacy, and pharmacokinetics across a wide dose range in BW

		dosing, assessment of the benefit-risk profile of a 240-mg flat dose relative to the approved 3-mg/kg dose was approached by quantitative clinical pharmacology.
	Data Availability	Clinical dose ranging data with 1 to 10 mg/kg in MEL, NSCLC and RCC, Established safety and tolerability at 10 mg/kg Q2W,
	Modeling / Analysis Method	A flat dose of 240 mg was selected based on its equivalence to the 3-mg/kg dose at the median BW of ~80 kg in patients in the nivolumab program. The benefit-risk profile of nivolumab 240 mg was evaluated by comparing exposures at 3 mg/kg Q2W and 240 mg Q2W across BW and tumor types using population PK analysis; predication of risk of experiencing adverse events (safety) and hazard of death (efficacy) at 240 mg Q2W relative to 3 mg/kg Q2W in melanoma, NSCLC, and RCC by Cox-proportional hazard modeling.
	Results	The median nivolumab exposures and its distribution at 240 mg Q2W were similar to 3 mg/kg Q2W in the simulated population. The predicted risk of safety and efficacy were similar across nivolumab exposure ranges achieved with 3 mg/kg Q2W or 240-mg Q2W flat dose.
	Inference /Simulation / Extrapolation	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.
	References / Acknowledgements	Zhao X, Suryawanshi S, Hruska M, Feng Y, Wang X, Shen J, McHenry B, Waxman I, Achanta A, Bello A, Roy A, Agrawal S. Assessment of nivolumab benefit-risk profile from a 240-mg flat dose versus a 3-mg/kg dosing regimen in patients with solid tumors. 2016 European Society of Medical Oncology. Annals of Oncology (2016) 27 (6): 359-378
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Risk/Benefit
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	High (Replace)

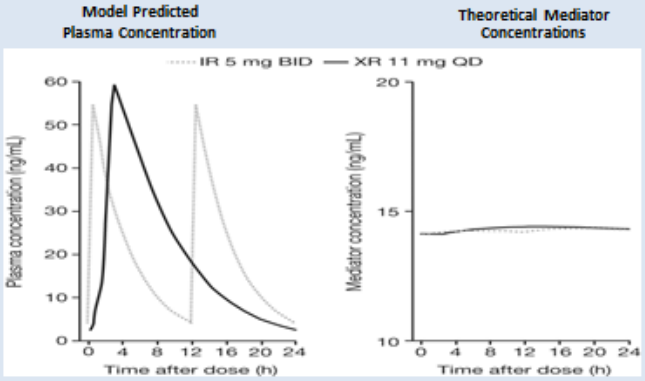
Regulatory Decision Making, Case Study #3

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

Regulatory Decision-making

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

Lamba M et al, CPT DOI: 10.1002/cpt.576; FDA. Guidance for industry. Providing clinical evidence of effectiveness for human drug and biological products. http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can QP and Model Informed Drug Development approaches help in regulatory approval of a new formulation/dosing regimen of tofacitinib, without a Phase III study?
	Quantitative Pharmacology-informed conclusion	The series of exposure-response (E-R) analyses conducted using data from clinical and nonclinical sources demonstrated that average concentration over the dosing interval (C_{av}) is the relevant pharmacokinetic (PK) parameter for tofacitinib efficacy. E-R analyses and PK studies provided the evidence to conclude that efficacy of tofacitinib extended release (XR) will be similar to that of tofacitinib immediate release (IR), thereby serving as the basis for registration without a Phase III study.
	Application Area	Regulatory decision-making, Dose/Schedule justification
Case study Details	Background / Introduction	We are presenting a case study of the application of a translational E-R modelling approach, in lieu of a Phase 3 trial, to support the registration of an XR formulation of tofacitinib, a Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). The approach is consistent with FDA guidance on clinical effectiveness with regards to the potential for well understood E-R relationships to provide the necessary evidence base but this provision has been rarely utilized and development programs for new formulation/dosage regimens

		typically has required a Phase III randomized controlled trial. The approval of tofacitinib XR 11 mg tablets by the FDA earlier this year followed the original approval of (IR) 5 mg tablets twice daily (BID) in 2012.
	Data Availability	Data from multiple sources were analyzed that included Phase 2 dose-ranging studies of the IR formulation in the patient population and nonclinical dose ranging data from murine model of inflammation.
	Modeling / Analysis Method	The clinical E-R analyses included data from approximately 1,350 patients with RA, encompassing a 30-fold dose range of tofacitinib IR (1-30 mg BID and 20 mg QD) and treatment durations ranging from 6–24 weeks. Well validated clinical endpoints were used for these analyses. A series of E-R analyses were conducted to: a) estimate the degree of hysteresis in dynamics of efficacy response relative to PK; b) evaluate the importance of C_{min} differences to efficacy of tofacitinib when the IR formulation was administered as QD or BID; c) delineate the predictive abilities of Cmax, Cav, and Cmin for efficacy endpoints; d) provide corroborative evidence of the most relevant PK parameter of efficacy from nonclinical model
	Results	A variety of QP approaches showed that 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 /Simulation / Extrapolation	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	Innovative strategy where PK/PD based analyses in conjunction with PK data formed the basis of benefit:risk assessment of the XR formulation. 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.
	References / Acknowledgements	1. Lamba et al, Model-informed Development and Registration of a Once-daily Regimen of Extended-release Tofacitinib, CPT DOI: 10.1002/cpt.576 2. FDA. Guidance for industry. Providing clinical evidence of effectiveness for human drug and biological products. Available at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Risk/Benefit
	MID3 Level	Compound
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	High (Replace)

Regulatory Decision Making , Case Study #4

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

Regulatory Decision-making

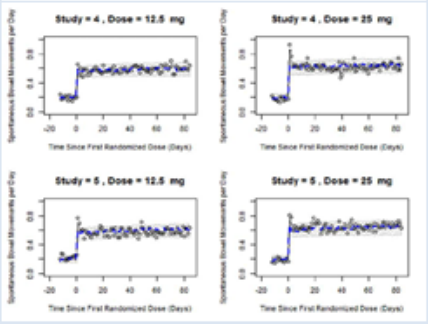
Key Question: Does lowering the dose from 25 to 12.5 mg naloxegol provide benefit in patients with opioid-induced constipation?

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 (α=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

Al-Huniti et al CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 359–366

Contactperson: diansong.zhou@astrazeneca.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Does lowering the dose from 25 to 12.5 mg naloxegol provide benefit in patients with opioid-induced constipation?
	Quantitative Pharmacology-informed conclusion	Provide supportive evidence of efficacy in a population that may retain benefit with the lower 12.5 mg naloxegol, if 25 mg cannot be tolerated, and facilitate approval of the lower dose in patients with opioid-induced constipation
	Application Area	Regulatory decision-making, Dose/Schedule justification
Case study Details	Background / Introduction	Naloxegol is a peripherally acting μ-opioid receptor antagonist for the treatment of opioid-induced constipation. 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 (α=0.05,

		p=0.202 and p=0.015) in one of the phase 3 trials.
	Data Availability	Phase 3 studies
	Modeling / Analysis Method	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.
	Results	Predicted placebo-adjusted responder rates (90% confidence interval) were 10.4% (4.6%-13.4%) and 11.1% (4.8%-14.4%) for naloxegol 12.5 and 25 mg/day, respectively, indicating the 12.5 mg dose thus provided a clinical benefit over placebo with comparable efficacy to the 25 mg dose.
	Inference /Simulation / Extrapolation	Inference
	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.
	References / Acknowledgements	Al-Huniti et al., Population Exposure-Response Modeling of Naloxegol in Patients With Noncancer-Related Pain and Opioid-Induced Constipation *CPT Pharmacometrics Syst. Pharmacol.* 2016; 5: 359–366
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Risk/Benefit
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium (Justify)

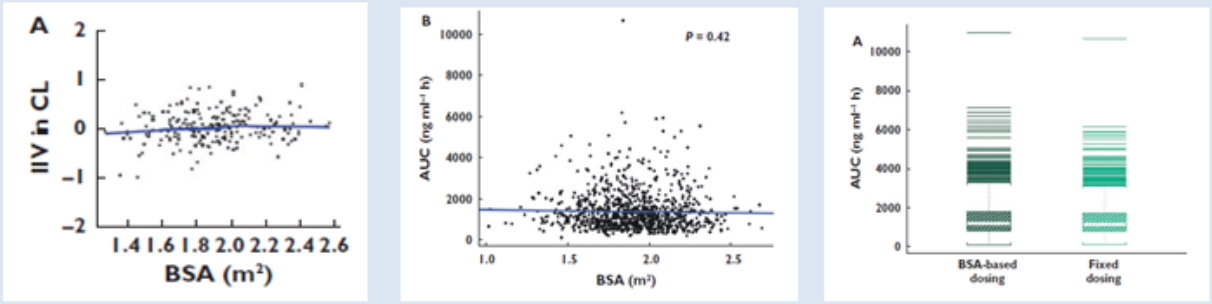
Regulatory Decision Making, Case Study #5

Switch from BSA-based to fixed dosing simplified dosing guidance and clinical development — Regulatory Decision-making

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.

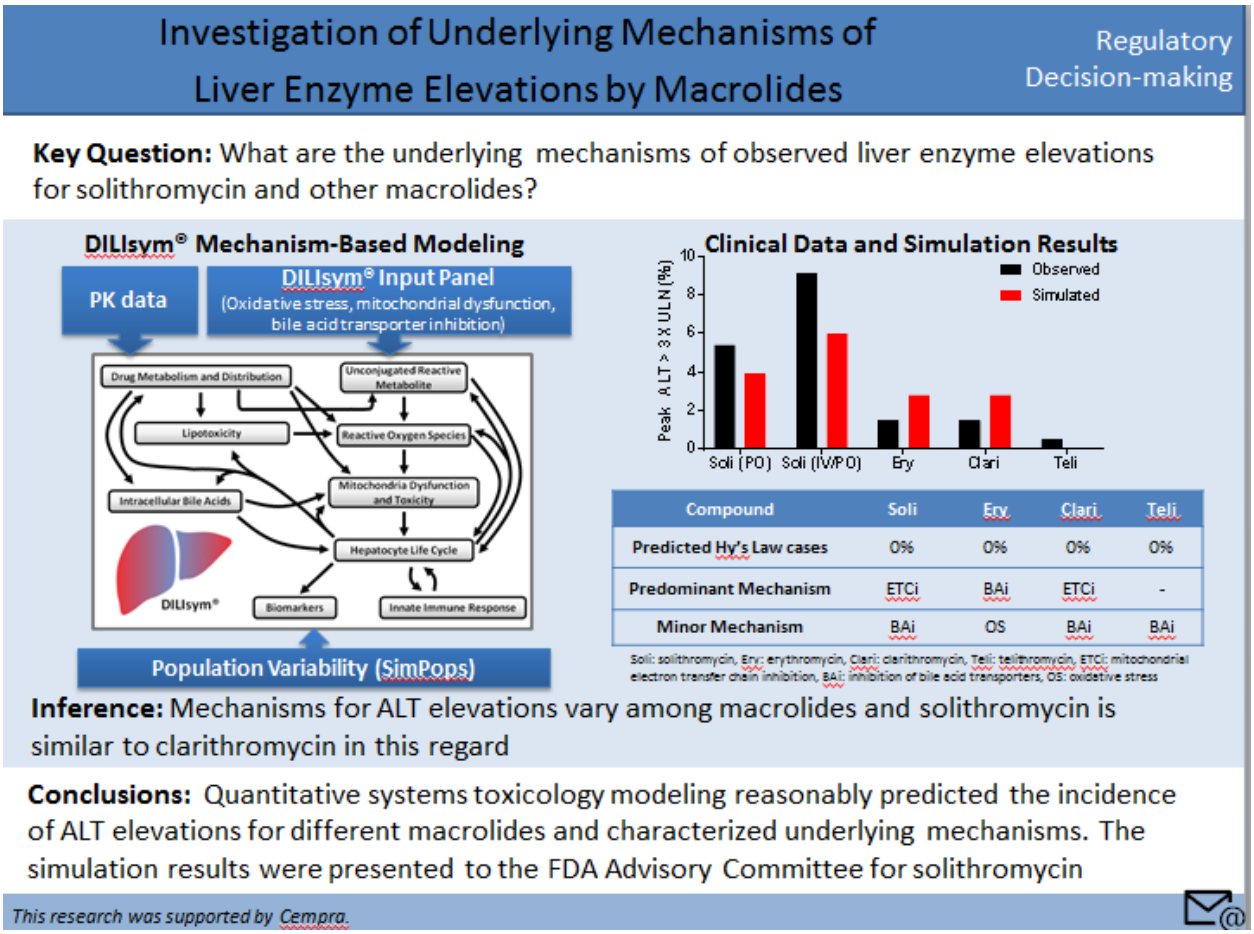
Gupta N, Zhao Y, Hui AM, Esseltine DL, Venkatakrishnan K. Br J Clin Pharmacol.79(5):789-800 (2015)

Contactperson: Neeraj.Gupta@Takeda.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	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?
	Quantitative Pharmacology-informed conclusion	This model based analysis supported a switch from BSA-based to fixed dosing without need for a dedicated study to compare fixed dose vs BSA based dosing. 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.
	Application Area	Regulatory decision-making, Dose/Schedule justification
Case study Details	Background / Introduction	This population pharmacokinetic analysis of an oral proteasome inhibitor ixazomib assessed the feasibility of switching from body surface area (BSA)-based to fixed dosing.
	Data Availability	Data were pooled from 226 adult patients with multiple myeloma, lymphoma, or solid tumors in four phase 1 studies, in which ixazomib dosing (oral/intravenous, once/twice weekly) was based on BSA.
	Modeling /	Population pharmacokinetic modelling was done using NONMEM version 7.2.

	Analysis Method	
	Results	Ixazomib pharmacokinetics were well described by a three-compartment model with first-order absorption and linear elimination. Ixazomib was absorbed rapidly (Ka 0.5 h-1), with dose- and time-independent pharmacokinetics. Estimated absolute bioavailability and clearance were 60% and 2 l h-1, respectively. Although a small effect of BSA (range, 1.3–2.6 m2) was observed on the peripheral volume of distribution (V4), reducing the corresponding inter-individual variability by 12.9%, there was no relationship between BSA and ixazomib clearance.
	Inference /Simulation / Extrapolation	Based on simulations (N = 1000), median AUCs (including interquartile range) were similar after BSA-based (2.23 mg m 2) and fixed (4.0 mg) oral dosing with no trend in simulated AUC vs. BSA for fixed dosing (p = 0.42).
	Conclusions	Analysis supported a switch from BSA-based to fixed dosing in future adult studies of ixazomib, simplifying dosing guidance and clinical development. 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.
	References / Acknowledgements	Gupta N, Zhao Y, Hui AM, Esseltine DL, Venkatakrishnan K. Switch from BSA-based dosing to fixed dosing for the investigational drug MLN9708 (Ixazomib): Population pharmacokinetic model-based analysis to influence posology decisions in oncology drug development. Br J Clin Pharmacol.79(5):789-800 (2015)
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Efficacy
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium

Regulatory Decision Making, Case Study #6



Contactperson: KYang@DILIsym.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What are the underlying mechanisms of liver enzyme elevations for solithromycin and other macrolides?
	Quantitative Pharmacology-informed conclusion	Quantitative systems toxicology modeling reasonably predicted the incidence of alanine aminotransferase (ALT) elevations for different macrolides and characterized underlying mechanisms. The simulation results were presented to the FDA Advisory Committee for solithromycin on 11/4/16.
	Application Area	Regulatory decision-making, Risk/Benefit evaluation
Case study Details	Background / Introduction	Solithromycin, a 4th generation macrolide developed for the treatment of community acquired pneumonia, caused serum liver enzyme (ALT) elevations in clinical studies. A quantitative systems toxicology tool, DILIsym, was used to predict the occurrence and mechanisms of ALT

		elevations for solithromycin, erythromycin, clarithromycin, and telithromycin.
	Data Availability	In vitro assays were performed to assess effects of the macrolides on bile acid transport, mitochondrial function, and oxidative stress.
	Modeling / Analysis Method	In vitro mechanistic data were integrated with physiologically-based pharmacokinetic modeling-based in vivo exposure using DILIsym; serum ALT responses were predicted in a simulated human population.
	Results	DILIsym reasonably predicted the incidence of ALT elevations observed for solithromycin, erythromycin, and clarithromycin; the predominant mechanism was reversible mitochondrial electron transport chain inhibition for solithromycin and clarithromycin, and bile acid transport inhibition for erythromycin. ALT elevations by telithromycin were only predicted at the highest observed exposure combined with noncompetitive inhibition of bile acid transporters.
	Inference /Simulation / Extrapolation	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 on 11/4/16.
	References / Acknowledgements	This research was supported by Cempra.
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory interaction
	MID3 Theme	Safety & tolerability
	MID3 Level	Mechanism
	MID3 Approach	Systems pharmacology and PBPK
	Low / Medium / High impact	High

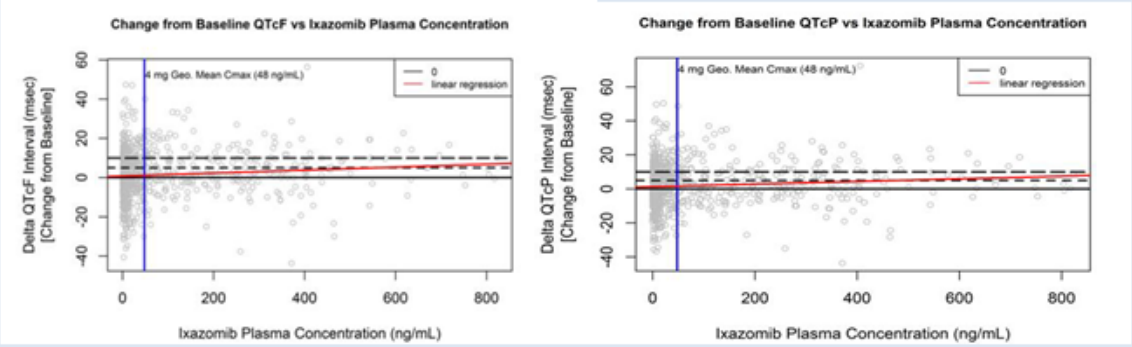
Regulatory Decision Making, Case Study #7

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

Regulatory Decision-making

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/m^2, N=125, solid tumors/lymphoma) or oral (0.24–3.95 mg/m^2, 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 ΔQTcF and mean ΔQTcP 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.

Gupta N, Huh Y, Hutmacher MM, Ottinger S, Hui AM, Venkatakrishnan K. Cancer Chemother Pharmacol. 2015 Sep;76(3):507-16. doi: 10.1007/s00280-015-2815-7

Contactperson: Neeraj.Gupta@Takeda.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can an integrated non-clinical and clinical risk assessment on the QTc interval for Ixazomib obviate the need for a dedicated clinical QTc study?
	Quantitative Pharmacology-informed conclusion	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.
	Application Area	Regulatory decision-making, Risk/Benefit evaluation
Case study Details	Background / Introduction	Integrated non-clinical and clinical assessment of ixazomib's effect on QTc intervals.
	Data Availability	Non-clinical studies assessed (1) the in vitro binding of ixazomib to the hERG channel, and (2) its effect on QT/QTc in dogs (N=4) via telemetry. 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.
	Modeling /	The relationship between ixazomib plasma concentration and heart-rate (HR) corrected

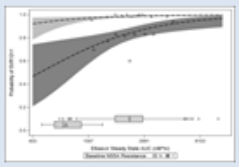
	Analysis Method	QT using Fridericia (QTcF) or Population (QTcP) methods was analyzed using linear mixed-effects models with fixed effects for day and time.
	Results	In vitro binding potency for ixazomib to the hERG channel was weak (Ki 24.9 µM; IC50 59.6 µM), and non-clinical telemetry studies showed no QT/QTc prolongation at doses up to 4.2 mg/m2. In cancer patients, ixazomib, when evaluated at doses yielding various plasma concentrations (with 26% of data greater than mean Cmax for the 4 mg phase III dose), had no meaningful effect on QTc based on model-predicted mean change in QTcF/QTcP from baseline. There was no relationship between ixazomib concentration and RR, suggesting no effect on HR.
	Inference /Simulation / Extrapolation	Predictions were computed for the steady-state geometric mean Cmax of 48 ng/ mL, achieved following repeat administration of the 4 mg weekly dose used in phase III trials. The predicted mean ΔQTcF and ΔQTcP (90 % CI) at the geometric mean Cmax achieved with the 4 mg dose were 0.0710 (–0.221, 0.363) and 0.0591 ms (–0.242, 0.361), respectively. Even 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 ΔQTcF and mean ΔQTcP 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 obviated the need for a dedicated QTc study in oncology. Ixazomib (ninlaro) was approved by FDA on Nov 20, 2015 and results from this analysis were included in the USPI of Ixazomib.
	References / Acknowledgements	Gupta N, Huh Y, Hutmacher MM, Ottinger S, Hui AM, Venkatakrishnan K. Integrated nonclinical and clinical risk assessment of the investigational proteasome inhibitor ixazomib on the QTc interval in cancer patients. Cancer Chemother Pharmacol. 2015 Sep;76(3):507-16. doi: 10.1007/s00280-015-2815-7. Epub 2015 Jul 4.
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Safety & Tolerability
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	High (Replace)

Regulatory Decision Making, Case Study #8

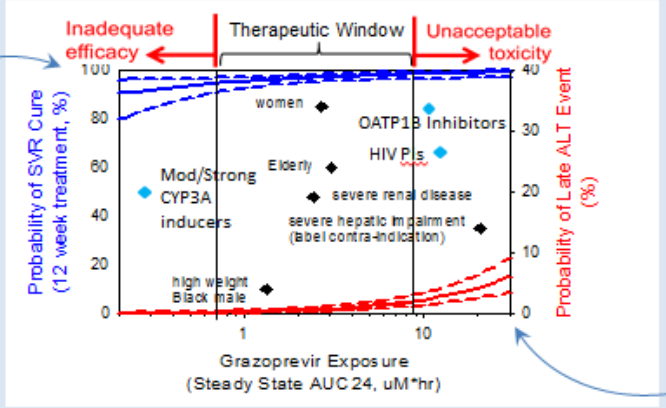
Limited label restrictions for drug interactions and demographics based on established therapeutic window — Regulatory Decision-making

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

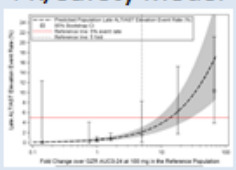
Data: ~2000 Patient Data + ~25 Phase I Drug Interaction or Sub-population Studies



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.

Caro, et. al. (2016, December). Application of Pharmacometrics for New HCV Drug Development - Ethnic Differences in PK. Presented at The Japanese Society of Clinical Pharmacology and Therapeutics, Yonago, Japan.

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Which drug interactions and demographic factor effects are clinically relevant and require dose adjustments or contraindications in the drug label?
	Quantitative Pharmacology-informed conclusion	Limited dose adjustments and contraindications in drug label based on wide therapeutic window established using safety and efficacy PK/PD analyses.
	Application Area	Regulatory decision-making, Label claims
Case study Details	Background / Introduction	MK-5172 demonstrated high efficacy at the therapeutic dose for patients assessed in Phase 2 and 3. However, the compound demonstrated safety findings at doses much higher than the therapeutic doses, and low non-therapeutic doses in HCV patients resulted in development of resistance. Therefore, there were concerns that subpopulations and DDIs that would

		results in increased or decreased exposures in HCV patients would result in dose adjustments or contraindications.
	Data Availability	Data from ~2000 HCV patients from Phase 2 and 3 were used for the PK/PD analysis. The same patient data plus healthy subject data from ~25 Phase I Drug Interaction or Sub-population Studies were used to estimate the change in PK exposure anticipated in patients.
	Modeling / Analysis Method	PK/PD analyses for safety and efficacy were used to define the upper and lower therapeutic bounds. Population PK analyses were used to estimate the change in PK exposure anticipated in patients.
	Results	The safety and efficacy PK/PD analyses provided an integrated understanding of exposure-response to establish the therapeutic bounds. The results demonstrated that despite safety findings at high exposures, the compound had a wide therapeutic window.
	Inference /Simulation / Extrapolation	Most drug interactions and demographic factors that effect drug exposure resulted in exposures within the therapeutic window, and therefore not clinically relevant.
	Conclusions	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
	References / Acknowledgements	Caro, *et. al.* (2016, December). *Application of Pharmacometrics for New HCV Drug Development - Ethnic Differences in PK*. Presented at The Japanese Society of Clinical Pharmacology and Therapeutics, Yonago, Japan.
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	Risk/Benefit
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium

Regulatory Decision Making, Case Study #9

PBPK modeling to support dosage recommendations for naloxegol drug-drug interaction labeling — Regulatory Decision-making

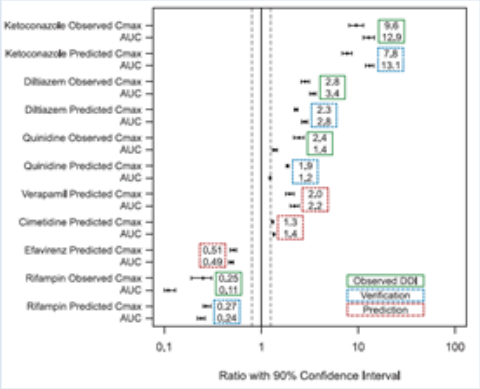
Key Question: How should naloxegol be prescribed to avoid potential drug-drug interactions?

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.

Zhou et al CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 250–257

Contactperson: diansong.zhou@astrazeneca.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How should naloxegol be prescribed to avoid potential drug-drug interactions?
	Quantitative Pharmacology-informed conclusion	Yes
	Application Area	Regulatory decision-making, Label Claims
Case study Details	Background / Introduction	Naloxegol is a peripherally acting μ-opioid receptor antagonist for the treatment of opioid-induced constipation and is a substrate for CYP3A4/3A5 and the P-gp transporter.
	Data Availability	Clinical pharmacology DDI studies
	Modeling / Analysis	By integrating in silico, preclinical, and clinical pharmacokinetic findings, minimal and full PBPK models were developed to predict

	Method	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%.
	Inference /Simulation / Extrapolation	Extrapolation
	Conclusions	In combination with clinical drug-drug interaction results, the PBPK model predicted results provided comprehensive dosage recommendations for naloxegol in the package insert.
	References / Acknowledgements	Zhou et al. Simulation and Prediction of the Drug-Drug Interaction Potential of Naloxegol by Physiologically Based Pharmacokinetic Modeling *CPT Pharmacometrics Syst. Pharmacol.* 2016; 5: 250–257
Additional Descriptions to link to MID3 Document applications	Development Phase	Regulatory Interaction
	MID3 Theme	PK
	MID3 Level	Compound
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	Medium (Justify)

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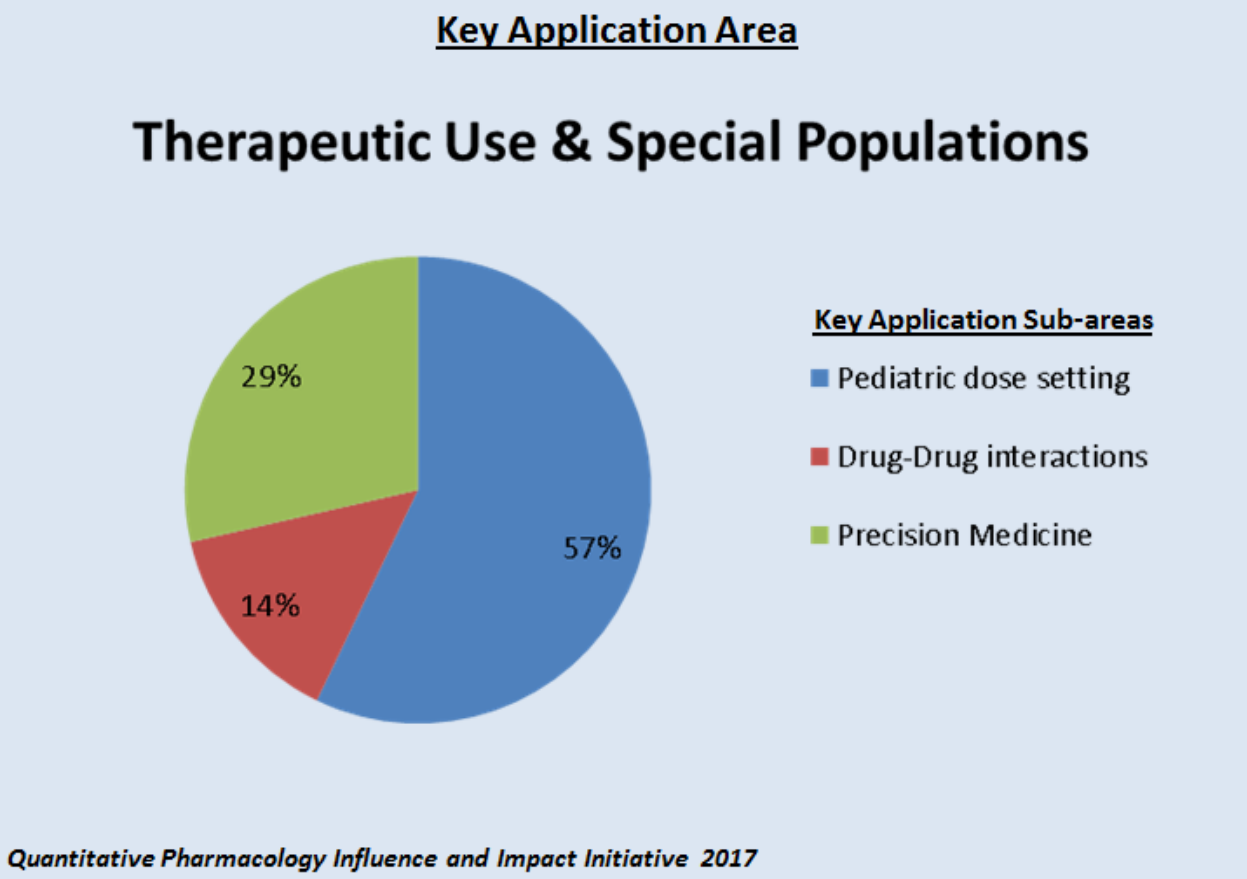


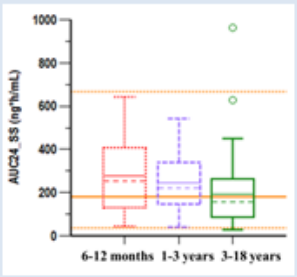
Therapeutic Use & Special Populations, Case Study #1

Modeling and simulation for clinical studies in pediatric populations

Therapeutic Use & Special Populations

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	Initialdose
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

Peigné et al,. J Pharmacokinet Pharmacodyn. 2016 Feb;43(1):13-27. doi: 10.1007/s10928-015-9451-z.

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How to determine the starting dose in children suffering from chronic heart failure?
	Quantitative Pharmacology-informed conclusion	This work emphasizes the importance of modelling and simulation for internal decision-making such as the design of clinical studies for drug development in paediatric populations. Without this approach, lower doses of ivabradine would have been chosen as first doses to be administered to children with the risk of insufficient efficacy for the children enrolled in the study.
	Application Area	Therapeutic Use and Special populations, Pediatric dose setting
Case study Details	Background / Introduction	The strategy implemented to select the initial dose in each age class was based on PBPK simulations (Simcyp®) of ivabradine concentration-time

		profiles, performed in the paediatric population, and aimed at achieving a similar exposure in children as in adults.
	Data Availability	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	The starting doses were proposed to be one dose level below the one in adult. Younger children were slightly more exposed compared to others; it was thus proposed to use a lower starting dose for this age group.
	Inference /Simulation / Extrapolation	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 worked allowed 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. Initial doses were proposed to be as follows: 0.05 mg/kg for 1-3 years and 3-18 years (with weight < 40 kg), 0.02 mg/kg for 6-12 months, and 2.5 mg for 3-18 years (with weight ≥40 kg).
	References / Acknowledgements	Peigné S, Bouzom F, Brendel K, Gesson C, Fouliard S, Chenel M. Model-based approaches for ivabradine development in paediatric population, part I: study preparation assessment. J Pharmacokinet Pharmacodyn. 2016 Feb;43(1):13-27. doi: 10.1007/s10928-015-9451-z.
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	Pharmacokinetics
	MID3 Level	Compound
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	Medium (Justify)

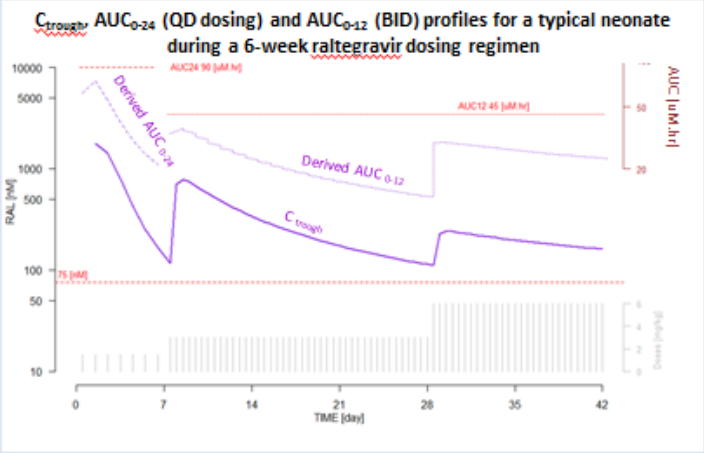
Therapeutic Use & Special Populations, Case Study #2

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.

Lommerse J, Clarke D, Chain A, et al. Raltegravir PK in Neonates – An Adaptive Trial Design to Define an Appropriate Regimen for Neonates from Birth to Six Weeks of Age. Presented at: ACoP 2016. Seattle, USA. J PKPD (2016) 43:S11–S122 T33

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Adequate 6 week dosing regimen of raltegravir in neonates
	Quantitative Pharmacology-informed conclusion	Adequate dosing regimen possible when allowing for 2 dose changes to account for dramatic increase of clearance as the result of UGT-1A1 maturation
	Application Area	Therapeutic Use and Special populations, Pediatric dose setting
Case study Details	Background / Introduction	3.2 million children are infected with HIV worldwide; of whom almost 800 die every day Mother-to-child HIV transmission is the most common route of HIV infection in newborn babies The World Health Organization (WHO) guidelines include raltegravir as an important product needed for certain pediatric populations Raltegravir has been approved for treatment of infants 4 weeks and older. Preferably treatment should start immediately after birth to continuously suppress viral replication without interruptions This case study summarizes the application of an adaptive trial design to define an adequate dosing regimen for neonates from birth up to 6 weeks

		of age
	Data Availability	PK data of 6 full-term infants received two 3 mg/kg doses of raltegravir (first dose within 48 hours after birth, second dose at 7-10 days of life). These neonate PK data of Cohort-1 were combined with the pediatric PK data of 24 HIV infected infants and children from the IMPAACT P1066 study
	Modeling / Analysis Method	Development of PopPK model in NONMEM
	Results	Using time-dependent clearance and absorption rate relationships, the population PK model described the observed data of the 6 neonates well.
	Inference /Simulation / Extrapolation	A daily dosing regimen to treatment neonates from birth up to 6 weeks of age was designed based simulations of the popPK model
	Conclusions	An adequate 6-week dosing regimen accounting for efficacy and safety PK criteria is possible when allowing for 2 dose changes addressing the dramatic increase of clearance as the result of UGT-1A1 maturation in neonate
	References / Acknowledgements	Lommerse J, Clarke D, Chain A, et al. Raltegravir dosing in neonates (IMPAACT P1110)—Use of allometry and maturation in PK modeling to develop a daily dosing regimen for investigation during the first weeks of life. Presented at: Population Approach Group Europe (PAGE) Conference. 2015. Hersonissos, Crete, Greece. Lommerse J, Clarke D, Chain A, et al. Raltegravir PK in Neonates – An Adaptive Trial Design to Define an Appropriate Regimen for Neonates from Birth to Six Weeks of Age. Presented at: American Conference of Pharmacometrics (ACoP). 2016. Seattle, USA.
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	Pharmacokinetics
	MID3 Level	Compound
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	Medium (Justify)

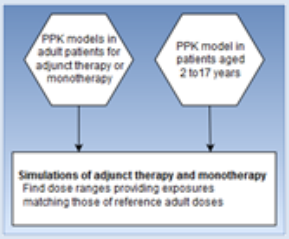
Therapeutic Use & Special Populations, Case Study #3

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

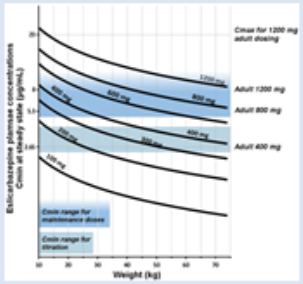
Therapeutic Use & Special Populations

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

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Which eslicarbazepine acetate (ESL) doses provide exposures in patients with partial-onset seizures (POS) aged 4 years and older that are similar to those determined to be safe and effective in adult patients for either adjunct therapy or monotherapy?
	Quantitative Pharmacology-informed conclusion	Model-based simulation of various dosing regimens in pediatric and adult patients supported the extrapolation of safe and effective doses from adult to pediatric patients.
	Application Area	Therapeutic Use and Special populations, Pediatric dose setting
Case study Details	Background / Introduction	ESL is approved by the US Food and Drug Administration (FDA) for adjunctive therapy and monotherapy in adult patients with POS. An analysis performed by the FDA Division of Clinical Pharmacology showed that, across multiple antiepileptic drugs, a similar exposure-response relationship exists in pediatric and adult patients with POS as well as a similarity of POS in pediatric patients 4 years of age and older and adults [1]. Effectiveness of ESL in adults could be extrapolated to patients 4 years of age and older by determining pediatric doses that provide exposures similar to those obtained with recommended doses in adults.

	Data Availability	Three Phase 3 clinical trials of ESL adjunctive therapy and 2 Phase 3 trials of ESL monotherapy supported definition of adult exposures associated with efficacy in POS; the pediatric population PK model was based on one Phase 2 and one Phase 3 ex-US clinical trials in pediatrics.
	Modeling / Analysis Method	Stochastic and deterministic simulations were performed using population pharmacokinetic models for ESL adjunct therapy in 4 to 17-year-old patients, and adjunct therapy in adult patients and monotherapy in adult patients [2]. Target exposures associated with efficacy in POS were set to the mean simulated minimum steady-state concentration (Cmin,ss) obtained at the recommended titration (400 mg QD) and maintenance doses (800 and 1200 mg QD) in adults receiving ESL adjunct therapy or monotherapy. Due to the absence of safety data in pediatric patients for daily doses above 1200 mg, the maximum effective range did not include exposures above this dose level (ie, ESL 1600 mg QD). Simulated Cmin,ss for ESL doses of 100 to 1600 mg QD were obtained in pediatric patients with body weights ranging from 10 to 74 kg receiving ESL adjunctive therapy or monotherapy.
	Results	By matching simulated pediatric exposures to target adult exposures, titration and maintenance doses of ESL were determined for discrete body weight ranges (<11, 11-21, 22-31, 32-38, and >38 kg).
	Inference /Simulation / Extrapolation	Based upon the similarity of POS in pediatric patients aged ≥ 4 y and adults, pediatric ESL doses could be extrapolated by targeting exposures proved to be safe and efficacious in adult patients using model-based simulation.
	Conclusions	Dose 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.
	References / Acknowledgements	[1] US Food and Drug Administration. 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
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	PK
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	High (Replace)

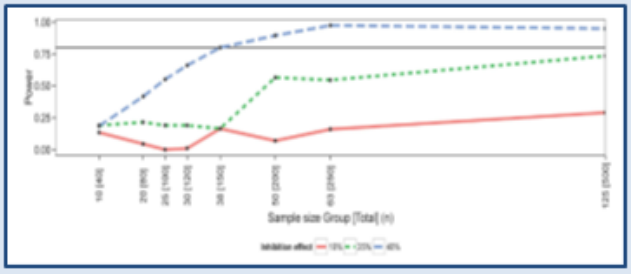
Therapeutic Use & Special Populations, Case Study #4

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

Therapeutic Use & Special Populations

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.

Van Hasselt et al. Pediatr Blood Cancer. 2014 Dec;61(12):2223-9.

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	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. The recruitment of sufficient patients is challenging and there were concerns about the impact of dropout and missing samples.
	Quantitative Pharmacology-informed conclusion	A feasible study design that could identify clinically relevant effects on vincristine clearance was identified and was used to support the clinical study protocol.
	Application Area	Therapeutic Use and Special populations, Pediatric dose setting
Case study Details	Background / Introduction	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 Availability	Adult population PK model, pediatric growth curves
	Modeling / Analysis Method	Clinical trial simulation, Mixed effect modeling
	Results	A study design with >38 patients per drug-condition could detect a clinically relevant effect of >40% inhibition of clearance.
	Inference /Simulation / Extrapolation	Simulation of missing PK samples, patient dropout, bodyweight and height
	Conclusions	An appropriate clinical trial design was identified.
	References / Acknowledgements	Van Hasselt et al. Pediatr Blood Cancer. 2014 Dec;61(12):2223-9.
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	PK
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium

Therapeutic Use & Special Populations, Case Study #5

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

Therapeutic Use & Special Populations

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

Data

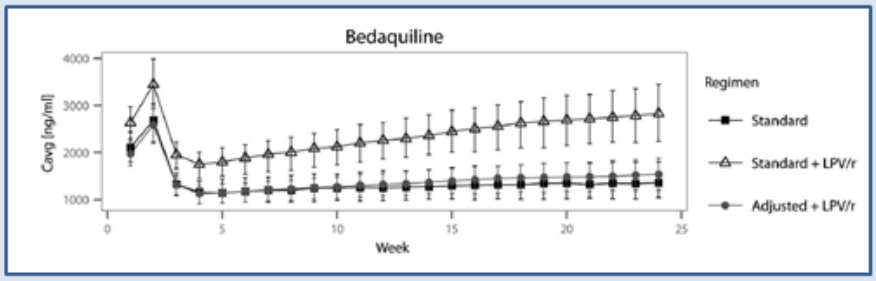
Concentrations of BDQ after single doses in a healthy volunteer drug-drug interaction study with LPV/r

Analysis Method

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

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



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.

EM Svensson et al., Antimicrobial agents and chemotherapy, 2014, 58 (11), 6406-6412

Contactperson: elin.svensson@farmbio.uu.se

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	How can bedaquiline (BDQ) safely be co-administered with ritonavir-boosted lopinavir (LPV/r)?
	Quantitative Pharmacology-informed conclusion	Dose reduction of bedaquiline needed to mitigate the drug-drug interaction with ritonavir-boosted lopinavir
	Application Area	Therapeutic Use & Special Populations, Drug-Drug interactions
Case study Details	Background / Introduction	Concomitant treatment of tuberculosis (TB) and HIV is recommended and improves outcomes. Bedaquiline is a novel drug for the treatment of multidrug-resistant (MDR) TB; combined use with antiretroviral drugs such as ritonavir-boosted lopinavir (LPV/r) is anticipated, but no clinical data from coinfected patients were available at the time of this analysis.
	Data Availability	Plasma concentrations of bedaquiline and its M2 metabolite after single doses were obtained from a cross-over interaction study with LPV/r in

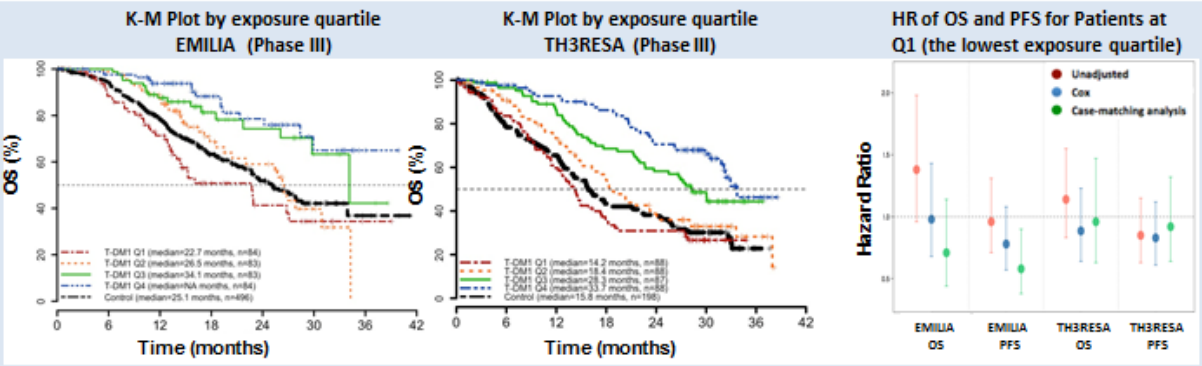
		healthy volunteers.
	Modeling / Analysis Method	The antiretrovirals' effects on bedaquiline and M2 pharmacokinetics were assessed by nonlinear mixed-effects modeling. Potential dose adjustments were evaluated with simulations.
	Results	LPV/r decreased bedaquiline and M2 clearances to 35% (relative standard error [RSE], 9.2%) and 58% (RSE, 8.4%), respectively, of those without comedication.
	Inference /Simulation / Extrapolation	The model-based estimates are predicting a much stronger effect compared to previously performed non-compartmental analysis. Almost 3-fold (bedaquiline) and 2-fold (M2) increases in exposures during chronic treatment with LPV/r are expected The safety of such exposures is unknown, hence dose adjustments are suggested for evaluation.
	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. The model-predicted impact has since been confirmed in clinical trials.
	References / Acknowledgements	Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection EM Svensson, KE Dooley, MO Karlsson Antimicrobial agents and chemotherapy 58 (11), 6406-6412 Pharmacokinetic Interactions for Drugs with a Long Half-Life—Evidence for the Need of Model-Based Analysis EM Svensson, C Acharya, B Clauson, KE Dooley, MO Karlsson The AAPS journal 18 (1), 171-179
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	PK
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium

Therapeutic Use & Special Populations, Case Study #6

Dose Optimization of Kadcyla (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer

Therapeutic Use & Special Populations

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.

Chen et al, Th3RESA ER, SABCS, 2016; Wang et al, EMILIA ER, ASCO, 2013

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	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)?
	Quantitative Pharmacology-informed conclusion	A dose optimization study in the patient subgroup with low T-DM1 exposure may not be warranted.
	Application Area	Therapeutic Use & Special Populations, Precision Medicine
Case study Details	Background / Introduction	An apparent ER trend was observed between model-predicted Cycle 1 Cmin and efficacy endpoints (ie PFS and OS) during EMILIA filing. As a result, a post-market requirement was issued to further assess the validity of the ER relationship in an ongoing Phase III study, TH3RESA. Results from these analyses were expected to inform whether a dose optimization study is needed for patients with lower T-DM1 exposure at the approved dose (3.6 mg/kg q3w)

	Data Availability	2 randomized Phase III studies were used: EMILIA (n=991) and TH3RESA (n=404)
	Modeling / Analysis Method	Kaplan-Meier analysis, multivariate Cox proportional-hazard analysis, Case matching analysis
	Results	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.
	Inference /Simulation / Extrapolation	After adjusting for baseline risk factors, T-DM1 provides numerically similar or better survival benefit (OS and PFS) to patients in Q1 compared with the active control, even though an apparent ER trend was observed for key efficacy endpoints (ie OS, PFS)
	Conclusions	Quantitative analysis enabled efficient decision making if a dose optimization study in patients with low T-DM1 exposure is needed for Kadcyla. The comprehensive ER analyses showed that, given favorable safety profiles, the approved T-DM1 dose (3.6 mg/kg q3w) has a positive benefit-risk profile over control, even for patients with low T-DM1 exposure, thus a dose optimization study in this patient subgroup may not be warranted.
	References / Acknowledgements	Chen et al, Th3RESA ER, SABCS, 2016; Wang et al, EMILIA ER, ASCO, 2013
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	Risk/Benefit
	MID3 Level	Compound
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	High

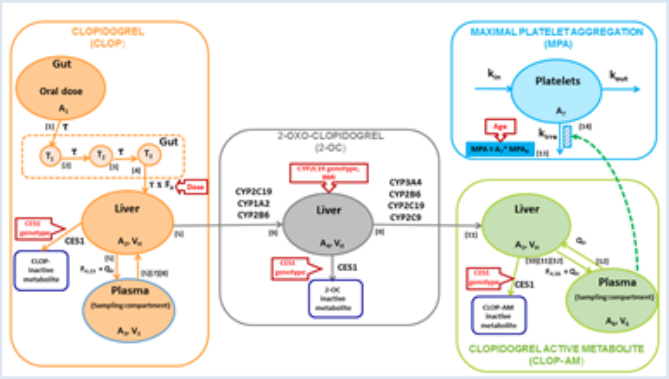
Therapeutic Use & Special Populations, Case Study #7

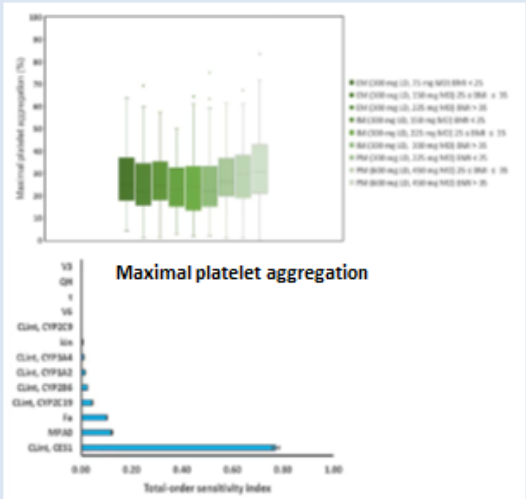
Identifying Clinically Relevant Sources of Variability: The Clopidogrel Challenge

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 (MPA0) are other sources of clinically significant variability in response to clopidogrel treatment.

Samant et al. Clin Pharmacol Ther. 2017; 101(2):264-273

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	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?
	Quantitative Pharmacology-informed conclusion	CYP2C19 LOF polymorphisms, BMI and age, interindividual differences in the fraction absorbed, CYP activity, CES1-mediated clearance, and in baseline platelet reactivity are the clinically relevant drivers of the interindividual variability in response to clopidogrel treatment. Higher clopidogrel dose is recommended for individuals with CYP2C19 loss of function and morbid and super obesity.
	Application Area	Therapeutic Use & Special Populations; Precision medicine
Case study Details	Background / Introduction	High interindividual variability in clinical outcomes following clopidogrel's standard dosing regimen continues to be a persistent challenge. CYP2C19 polymorphisms, obesity, older age, diabetes and drug-drug interactions have been identified as risk factors for adverse events and treatment failure. The objective of this study was to use an integrative approach of a mechanism-based population pharmacokinetic/pharmacodynamic (MB-POP-PK/PD) analysis to characterize the combined impact of multiple genetic and non-genetic covariates on clopidogrel's dose response relationship. The study also uses mechanistic insights and global sensitivity analysis to guide the identification of potential

		additional sources of between-subject variability.
	Data Availability	In vitro enzyme kinetics information from the literature were used for in vitro-in vivo correlation (IVIVC) of CYP mediated clopidogrel bioactivation. Clopidogrel and its active metabolite PK, platelet aggregation measurements and genetic and demographic information from 486 healthy Amish adults participating in the PGXB2B (NCT01341600) and the PAPI (NCT0079936) study were used for model development. Once developed, the model was externally qualified using a subset of 138 healthy adults from the PAPI study that were not used for model development.
	Modeling / Analysis Method	Information from in vitro enzyme kinetic studies, physiological processes, genetic (CYP2C19*2 and CES1 G143E polymorphisms), and demographic variables (age, body mass index (BMI)) was integrated into a unifying MB-POP-PK/PD model. The developed model was used to characterize changes in clopidogrel and its active metabolite exposures and platelet aggregation, as measured by ex-vivo light transmittance aggregometry, following clopidogrel dosing in healthy. adults. Sobol sensitivity analysis was performed to identify the most influential drivers of the variability in clopidogrel's PK/PD. The developed model was used to recommend personalized dosing strategies for subjects based on their CYP2C19 genotype and BMI.
	Results	The model simulations suggest higher maintenance doses are required for CYP2C19 intermediate (IMs) and poor metabolizers (PMs)compared to CYP2C19 extensive metabolizers (EMs) on standard CLOP dosing regimen and that respective maintenance doses have to be further increased for the morbid and super obese subjects for each of these CYP2C19 phenotypes Population analysis and global sensitivity analysis identified inter-individual differences in the fraction of oral dose absorbed, CES1 activity and baseline platelet reactivity as the other significant factors impacting clopidogrel PK/PD.
	Inference /Simulation / Extrapolation	The current mechanism-based modeling and simulation approach may help to prospectively design studies to identify sources of interindividual variability and guide optimal CLOP dosing strategies.
	Conclusions	A mechanism-based pop-PK/PD model characterizing the impact of CYP2C19 LOF polymorphisms, BMI and age, interindividual differences in the fraction absorbed, CYP activity, CES1-mediated clearance, and in baseline platelet reactivity on CLOP's dose-concentration-response relationship was developed. The model can be used to guide personalized CLOP dosing strategies based on the individual patient's CYP2C19 genotype and BMI
	References / Acknowledgements	
Additional Descriptions to link to MID3 Document applications	Development Phase	Life Cycle Management & Therapeutic Use,
	MID3 Theme	Risk/Benefit
	MID3 Level	Mechanism
	MID3 Approach	Semi-mechanistic PKPD
	Low / Medium / High impact	Medium (Justify)

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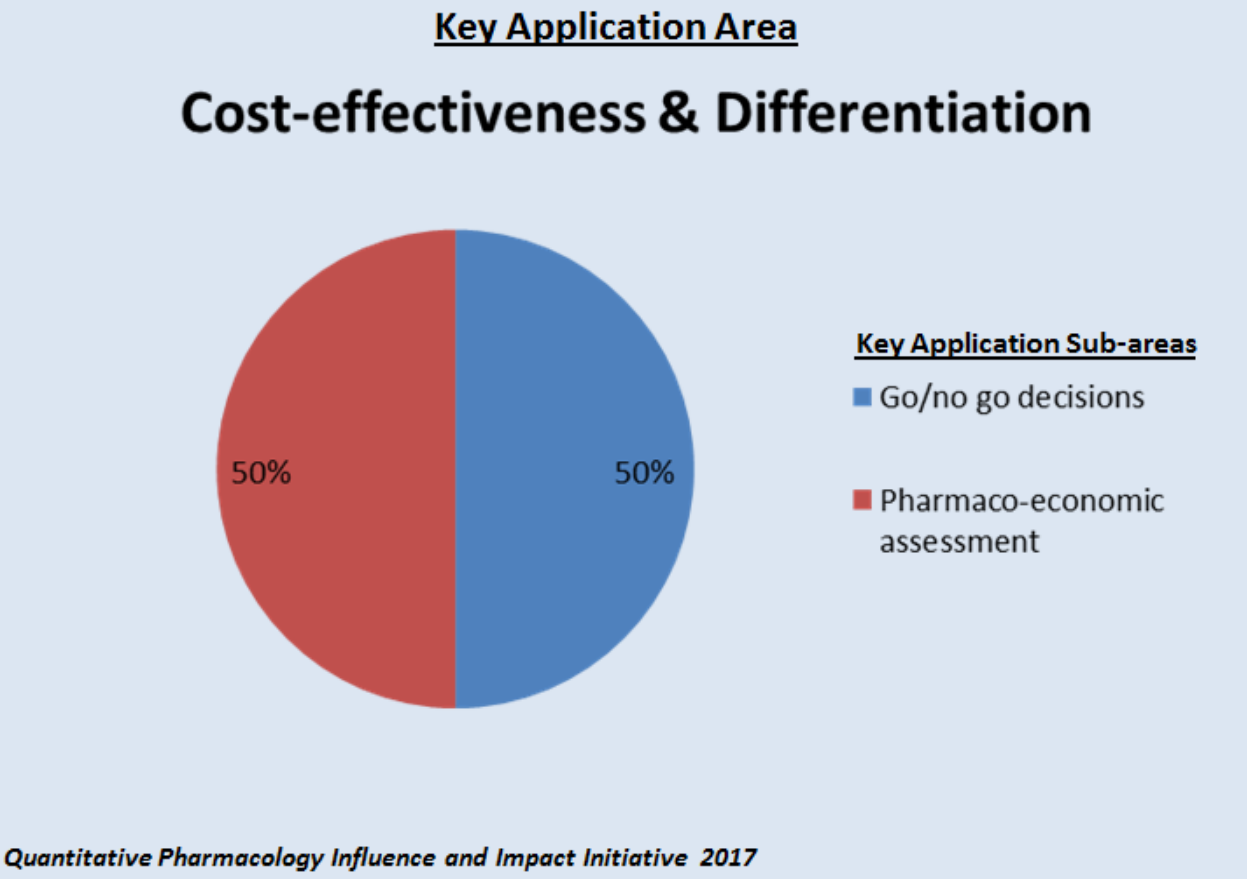
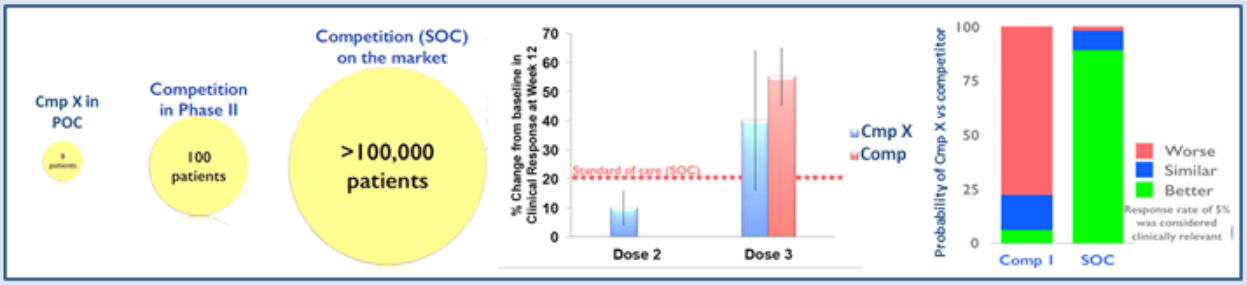


Cost Effectivenss & Differentitation, Case Study #1

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?



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

Bueters TJH et al, Informing Decisions in Discovery and Early Development Research Through Quantitative and Translational Modeling. From A Drug Candidate to the Clinic Today. F. Giordanetto (Ed.) Wiley-VCH Verlag GmbH & Co KGaA. In Press

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Does the compound have sufficient differential potential to SoC to support continuation of Ph1b POC study in patients?
	Quantitative Pharmacology-informed conclusion	Early No Go for compound based on limited differentiation potential compared to competitors
	Application Area	Cost-effectiveness & Differentiation, Go/no go decisions
Case study Details	Background / Introduction	For a disease, multiple competitors were developing novel approaches for a range of targets involved in the inflammatory response. Compound X was developed with the intention to become first-in-class to treat an inflammatory disease. Given the competition, an accelerated development program was proposed through a SAD in healthy subjects, followed by a combined Phase 1b MAD/POC study in patients to allow to directly moving into a Phase 2b dose finding stud

	Data Availability	Around the time of completion of the multiple ascending dose part (8 patients), a competitor published Ph2 data (~100 patients) on a compound with a related mechanism of action and similar indication. In addition, patient data (>100,000 patients) on Standard of Care was accessible in public domain.
	Modeling / Analysis Method	A model-based meta-analysis of the multiple ascending dose data and comparator data was conducted to assess the potential for differentiation
	Results	The analysis indicated that compound was effective and that adding more subjects would indeed increase the confidence on effect size. However, the analysis also showed that the onset of action and effect size was inferior to the competition for the clinical viable dose (i.e. the maximal dose that could be formulated).
	Inference /Simulation / Extrapolation	Simulations demonstrated that the probability of Compound X being comparable to that of the competitor was low without changes in clinical strategy, despite the fact that it would offer improvement over current standard of care. To complement the probabilistic analysis, expectations from new data (20 patients to be enrolled) were derived to claim differentiation from competitor.
	Conclusions	Quantitative analysis enabled efficient decision making on a moderately effective drug despite "little" data. Based on the limited available options to revise the clinical strategy and the competitor being substantially ahead in the development, the decision was made to not enroll more patients, and stop the program
	References / Acknowledgements	Bueters TJH, Gibson C, Kothare P, Lala M, Parker EM, Rizk ML, Tatiosian D, Trujillo ME, Vaddady P, Visser SAG. Informing Decisions in Discovery and Early Development Research Through Quantitative and Translational Modeling. From A Drug Candidate to the Clinic today. F. Giordanetto (Ed.) Wiley-VCH Verlag GmbH & Co KGaA. In Press
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Commercial viability
	MID3 Level	Compound
	MID3 Approach	MBMA
	Low / Medium / High impact	High

Cost Effectivenss & Differentitation, Case Study #2

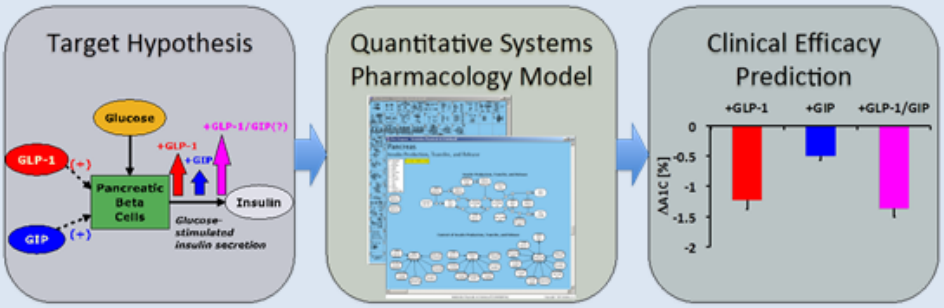
Early Decision to Terminate Program Based on Projected Lack of Differentiation from Other Anti-Diabetic Agents

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

Rieger and Musante. Eur. J. Pharm. Sci. Oct. 2016.

Contactperson: Ted.rieger@pfizer.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Can a dual GLP-1 + GIP agonist sufficiently differentiate from existing GLP-1 agonists for the treatment of type 2 diabetes?
	Quantitative Pharmacology-informed conclusion	Early No Go for compound based on limited differentiation potential compared to competitors
	Application Area	Cost-effectiveness & Differentiation, Go/no go decisions
Case study Details	Background / Introduction	The incretin hormones, primarily GLP-1 and GIP, are capable of stimulating the pancreas to secrete additional insulin per unit glucose. Numerous marketed therapies use various techniques to increase the concentration of GLP-1 in order to drive down plasma glucose and also lower body weight. Despite this robust improvement in the metabolic phenotype, high-dose GLP-1 injectables tend to cause nausea and other tolerability issues. This strong efficacy signal, but small tolerability window creates the potential for hitting the incretin axis from other avenues, including a combination of GLP-1 and GIP. While existing DPP-IV

		inhibitors do elevate both hormones, no existing therapy elevates both hormones to the level of the injectables, which is required for weight loss. An existing Systems Pharmacology model, the Entelos Metabolism PhysioLab, was updated to allow the simulation of a hypothetical dual GLP-1/GIP therapy. Previously this model had been calibrated to infusion data for both hormones in healthy normal volunteers. We assumed the PK of the dual agonist would be the same as liraglutide, a long-acting GLP-1 mimetic. For PD we chose a very high-level of exposure for GIP (ED97) to ensure the simulations were biased towards a false positive (proceed despite low efficacy) vs. a false negative (stop despite strong potential for efficacy). We simulated the effect(s) of 12-weeks of therapy for our dual incretin vs. liraglutide in a cohort of type 2 diabetes virtual patients.
	Data Availability	Extensive literature on incretin biology and their effects on both healthy volunteers and patients with T2D.
	Modeling / Analysis Method	Modeling and Simulation
	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 (clinically insignificant) as we increased the concentration of GLP-1.
	Inference /Simulation / Extrapolation	While some additional efficacy was predicted to be possible through dual incretin action, the added benefit was deemed insufficient to ensure differentiation from existing compounds for either efficacy or tolerability.
	Conclusions	Even though several optimistic assumptions around GIP's activity in patients with diabetes were made (see Rieger and Musante. 2016), the hypothetical dual incretin did not sufficiently differentiate from existing GLP-1 products to justify further investment. The Quantitative Systems Pharmacology model was a contributing piece that allowed the Project Team to make their recommendation with confidence to management.
	References / Acknowledgements	Rieger and Musante. Eur. J. Pharm. Sci. Oct. 2016. Acknowledgements: Cynthia Musante, Margaret Jackson, David Tess, and Danny Chen (Pfizer), Julie Jones (Novartis), Jeff Trimmer (Edison)
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Discovery
	MID3 Theme	Efficacy
	MID3 Level	Mechanism
	MID3 Approach	Systems Pharmacology and PBPK
	Low / Medium / High impact	High

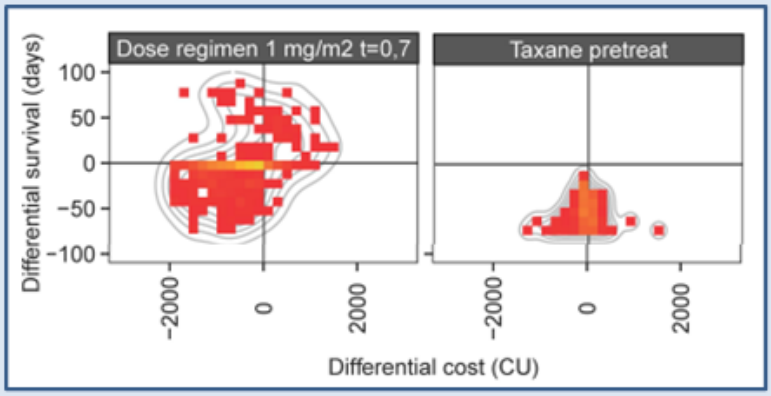
Cost Effectivenss & Differentitation, Case Study #3

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

Cost-Effectiveness & Differentiation

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

Van Hasselt et al. CPT Pharmacometrics Syst Pharmacol. 2015 Jul;4(7):374-85

Contactperson: coenvanhasselt@gmail.com

Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	What is the impact of dose regimens, different patient populations, and trial design on cost-effectiveness of anti-cancer agents?
	Quantitative Pharmacology-informed conclusion	Dose regimens, patient populations and trial design can significantly impact differential cost-effectiveness outcomes.
	Application Area	Cost-effectiveness & Differentiation, Pharmacoeconomic assessment
Case study Details	Background / Introduction	Anti-cancer drug efficacy and health care costs are strongly associated with drug toxicity profiles. Its consideration is therefore important to obtain realistic estimates of efficacy and cost-effectiveness.
	Data Availability	Multiple clinical studies across indications for the anti-cancer drug eribulin

	Modeling / Analysis Method	Combined simulations of multiple mixed effect models
	Results	Simulated survival and toxicity events for different dosing/trial/population scenarios.
	Inference /Simulation / Extrapolation	Differential survival (efficacy) and expected cost-effectiveness
	Conclusions	The use of a PKPD based approach to evaluate the expected effect of different dose regimens, patient populations or trial designs allow mechanism-based cost-effectiveness optimization in early drug development.
	References / Acknowledgements	Van Hasselt et al. CPT Pharmacometrics Syst Pharmacol. 2015 Jul;4(7):374-85 Van Hasselt et al. CPT Pharmacometrics Syst Pharmacol. 2015 Jul;4(7):386-95 Van Hasselt et al. Br J Clin Pharmacol. 2013 Sep;76(3):412-24.
Additional Descriptions to link to MID3 Document applications	Development Phase	Drug Development
	MID3 Theme	Commercial viability
	MID3 Level	Disease
	MID3 Approach	Empirical PKPD
	Low / Medium / High impact	Medium

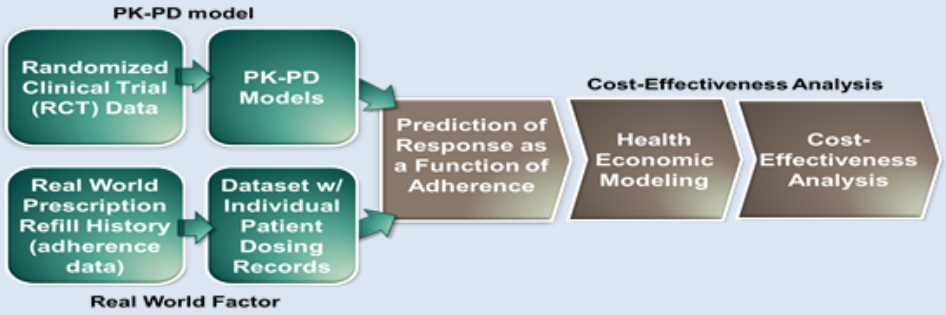
Cost Effectivenss & Differentitation, Case Study #4

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

Jain L, Chen J, Lala M, Davis C, Liu J, Chain A, Tatosian T, Liu Y, Visser SA, Tunceli K, Mavros P, Jadhav P. Integration of PK-PD and Health Economic Modeling to Assess Cost-Effectiveness of Improving Adherence in Real World Setting. Poster at ASCPT 2016

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Case study Descriptors		Description
Application Question and Impact	Key Question Addressed	Would a hypothetical new drug/technology offering better adherence for a diabetes drug be more cost-effective compared to existing standard of care?
	Quantitative Pharmacology-informed conclusion	Early prediction of cost-effectiveness and differentiation potential of a new compound without generating actual clinical efficacy data
	Application Area	Cost-effectiveness & Differentiation, Pharmacoeconomic assessment
Case study Details	Background / Introduction	Using a diabetes drug as an example, a framework to integrate PK-PD Models with Health Economic Models was established. To demonstrate the application, this integrated approach was used to assess the cost-effectiveness for a hypothetical new drug which exhibits treatment adherence improvement
	Data	Dose and Hba1c response data for a once-daily diabetes drug were used

	Availability	to link dose with HbA1c response. This was combined with the real-world adherence data for this drug from a prescription refill history dataset to predict the change in HbA1c response as a function of adherence.
	Modeling / Analysis Method	A PK-PD model linking dose with HbA1c response was developed with clinical data. Real-world prescription refill history dataset was converted into a dataset with dosing records for each subjects (e.g., NONMEM ready dataset) based on Beta and Binominal distribution assumption for number of missed days (ie, gaps). Integration of PK-PD model and real-world data allowed prediction of change in hbA1c response by adherence improvement. This was incorporated in Health Economic Model to assess improvement in cost-effectiveness for different scenarios of adherence improvement.
	Results	In subjects who were less adherent at baseline (<80% adherence) to the current standard of care, the new hypothetical drug providing better adherence had potential to improve cost-effectiveness. However, less than half of the population had <80% adherence at baseline
	Inference /Simulation / Extrapolation	There is an opportunity to integrate predictive models such as *PK-PD Models* with *Health Economic Models* to enable robust evaluation of cost-effectiveness with limited clinical data
	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
	References / Acknowledgements	Lokesh Jain, Jieling Chen, Mallika Lala, Casey Davis, Jinan Liu, Anne Chain, Daniel Tatosian, Yanhui Liu, Sandra Visser, Kaan Tunceli, Panagiotis Mavros, Pravin Jadhav. Integration of PK-PD and Health Economic Modeling to Assess Cost-Effectiveness of Improving Adherence in Real World Setting. Poster at ASCPT 2016
Additional Descriptions to link to MID3 Document applications	Development Phase	Therapeutic use
	MID3 Theme	Commercial viability
	MID3 Level	Disease
	MID3 Approach	Empirical PKPD, Health Economic Model
	Low / Medium / High impact	Medium