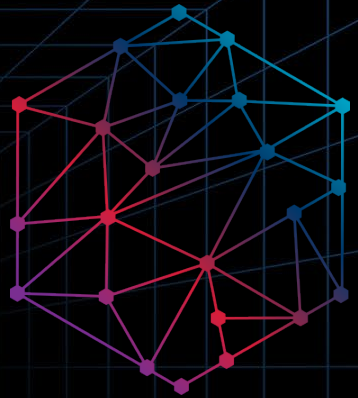
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Welcome and Introduction

Shawn O'Connor, CEO of Simulations Plus

Brett Howell, President of DILIsym Services Divsion

SimulationsPlus

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MIDD+ Conference Evolution:

Evolving relationship between M&S and pharma R&D

- Model “supported” (questions 20 years ago):
  - *Do you think modeling and simulation might help?*
- Model “based” (questions 5 years ago):
  - *How can I maximize the value of modeling and simulation in my development program?*
- Model “informed” (questions AND ANSWERS today!):
  - *How do I change the entire R&D process to reflect the availability of M&S tools and techniques?*

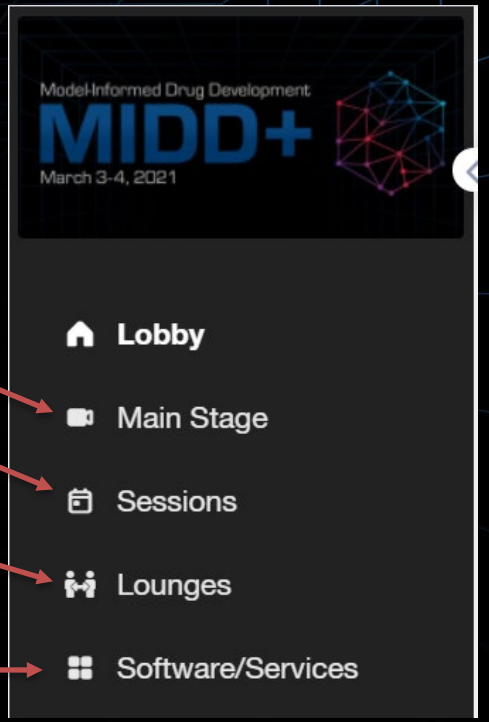
MIDD+ Conference Agenda

- Wednesday, March 3rd 11 AM – 3 PM EST
  - Impact of Modeling Panel Discussion
  - Tracks: Discovery, Pre-clinical, FIH/Phase I
  - The Model Student Sessions for Professors & Students
- Thursday, March 4th 11 AM – 3 PM EST
  - Women in Science Roundtable
  - Tracks: Phase II, III, and Post-Approval/Generics
  - 2021 MIDD+ Awards Ceremony

MIDD+ Conference Portal

Use the event portal to navigate through the conference:

- Watch keynote, panel & roundtable discussions on the Main Stage
- Find Sessions & Speakers easily
- Celebrate Dr. Bob Clark's retirement in the Lounge
- Learn more about our solutions and speak to a company representative



SimulationsPlus

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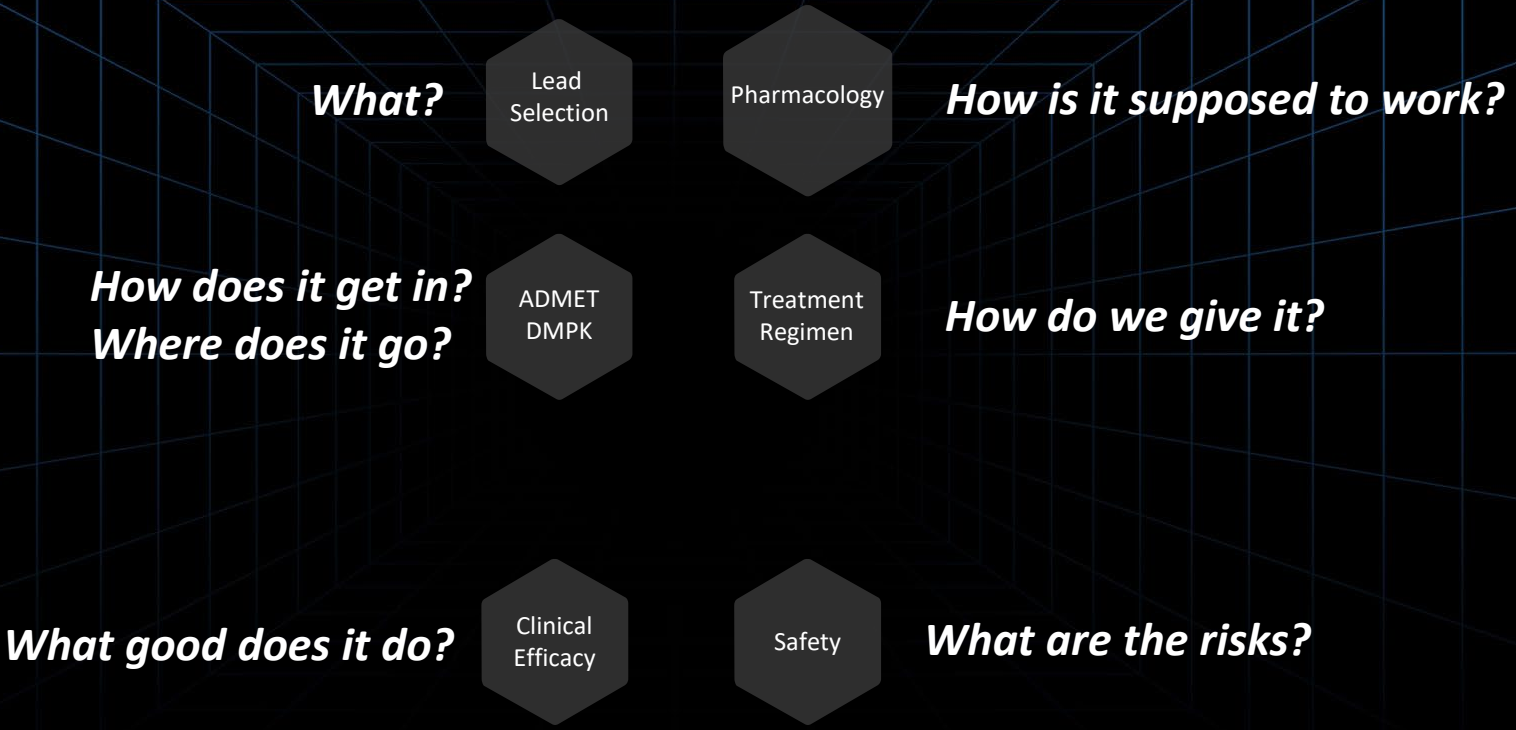
Who Are We?

Drug Product Developers Need to Answer Questions



Success is Measured in the Big Picture

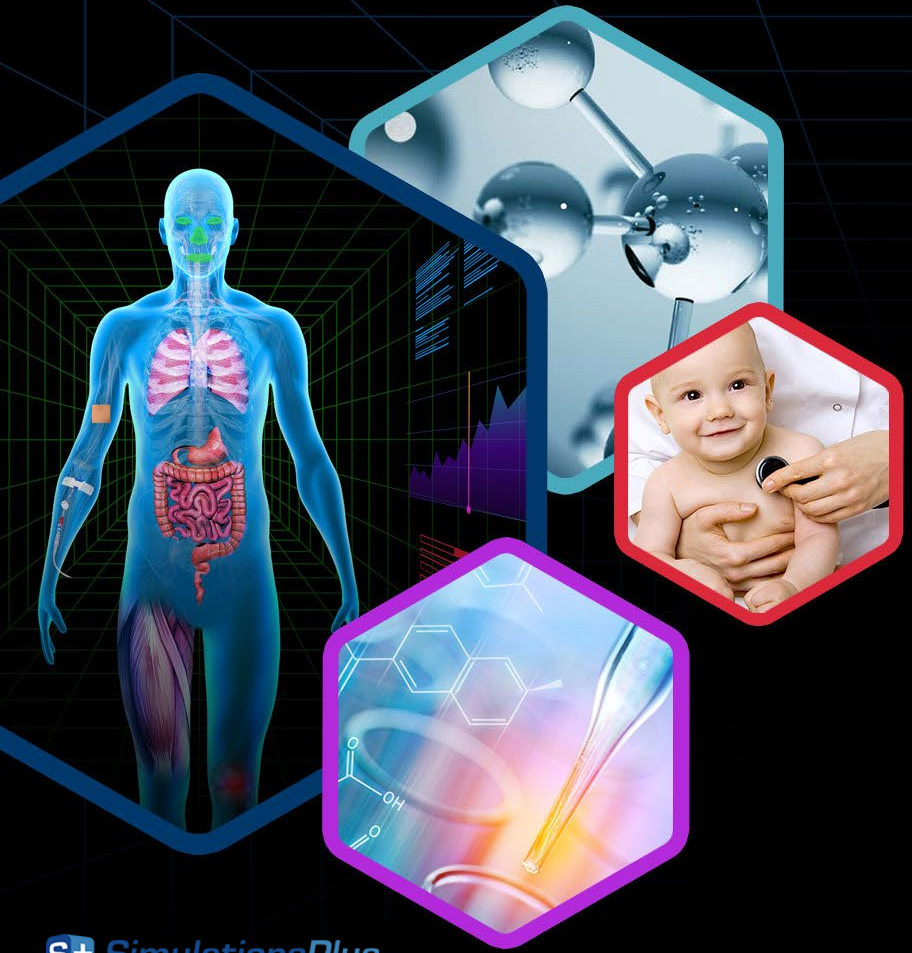
Regulatory Success

Efficiency

Patient Benefit

Commercial Success

About *SimulationsPlus*



Vision & Mission

Vision

To improve health through innovative solutions

Mission

Our mission is to create value for our customers by accelerating and reducing the costs of R&D through innovative science-based software and consulting solutions
that optimize treatment options
and improve patient lives

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Values

Innovation

Pursuing novel and creative solutions
to positively impact the world

Respect

Promoting a diverse workforce and inclusive culture,
while serving our communities

Integrity

Thoroughly and accurately communicating
with uncompromised truth and honesty

Commitment

Providing quality products and exceptional services
that deliver value to our partners and the people we serve

S+ SimulationsPlus
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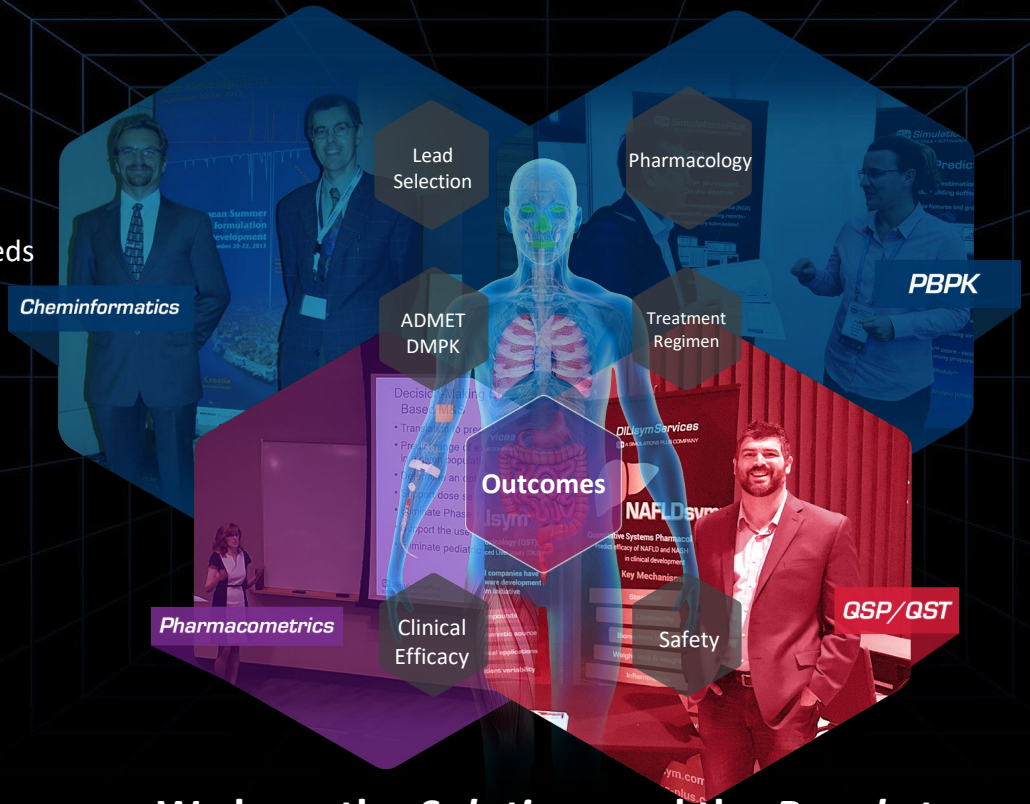
At *SimulationsPlus* We Put It All Together

Science

- Seamless collaboration
- Integrated, innovative solutions to meet <u>your</u> needs



Business

- Resources available to get the job done on time
- One-stop shopping – single vendor for all of your *in silico* drug development needs

We have the *Solutions* and the *People* to Address *<u>Your</u>* Drug Development Questions!

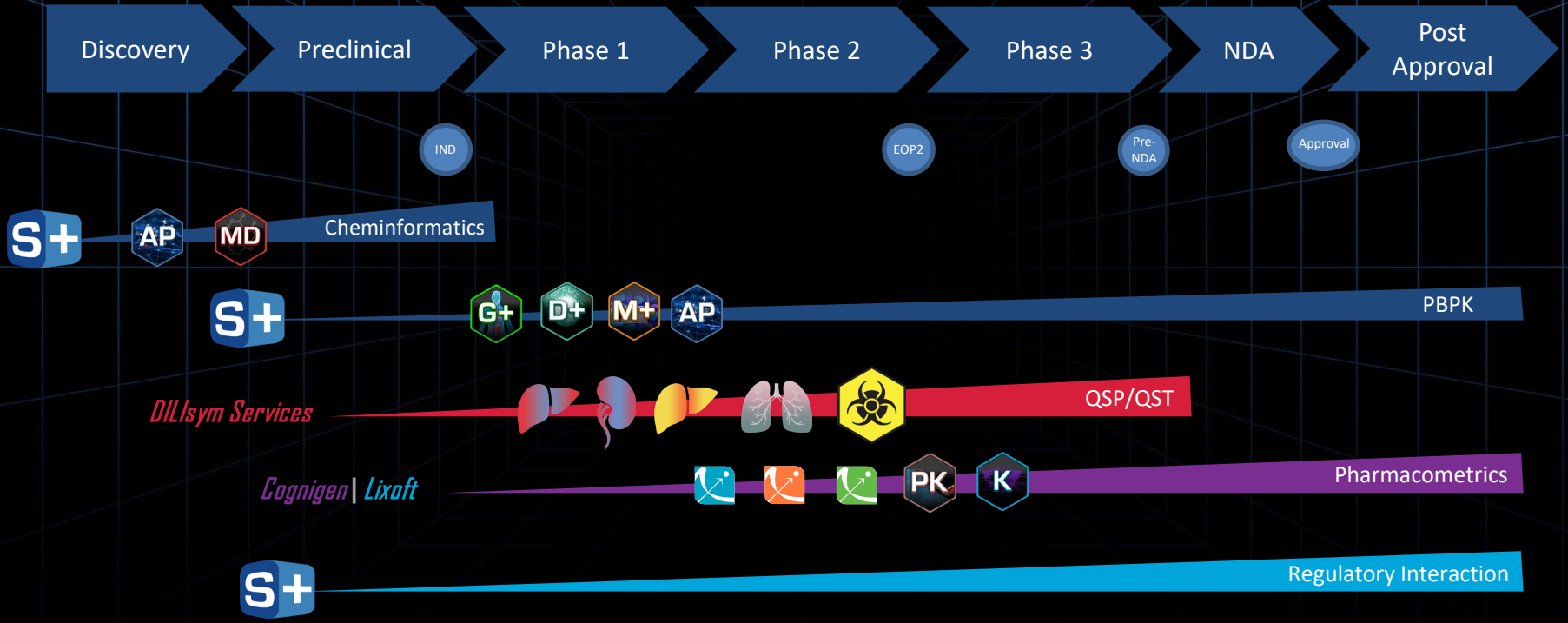
How We Can Help: Two Sides to the Company

Software: The most comprehensive and widely recognized set of tools for *in silico* drug development. Ongoing development and reinvestment to incorporate the latest science and ensure a seamless user experience.

Services: Highly interactive collaboration with our renowned experts allows us to deliver results in timely fashion and ensures a top quality deliverable.

- Regular interactions and frequent progress updates eliminate surprises and ensure relevance as the knowledge-base evolves
- Synergies come from shared knowledge between client and consultant
- We welcome involvement, participation, and input from stakeholders outside of M&S

Our solutions inform the entire drug development process



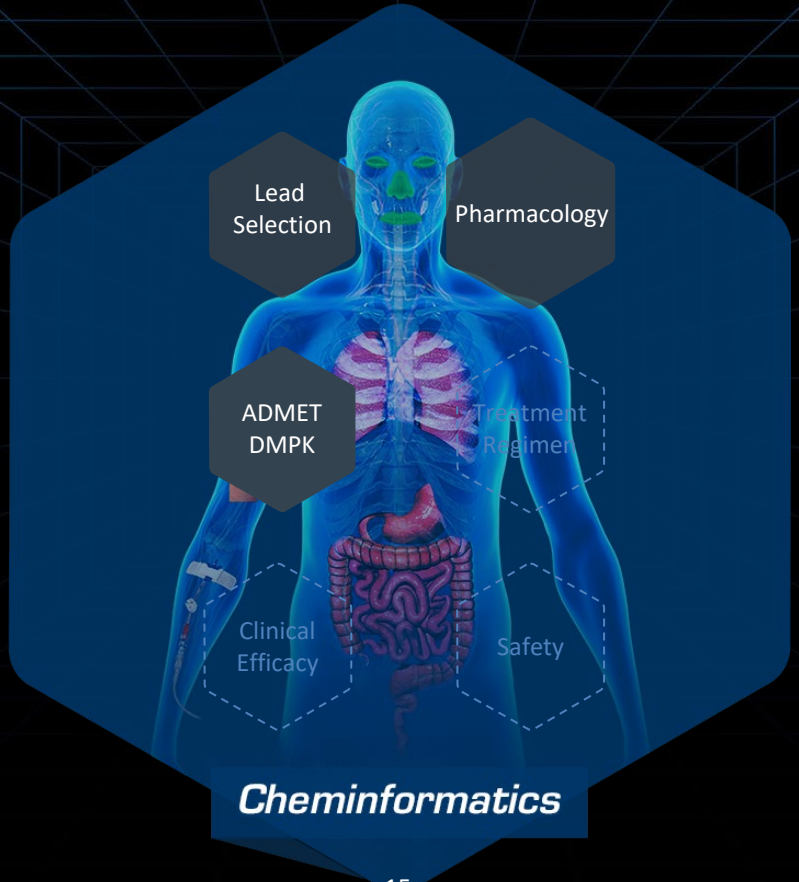
Our *Cheminformatics* Solutions Help Find the Right "Drugable" Candidate

Software

ADMET Predictor®
MedChem Designer™
HTPK
AIDD/Machine Learning

Services

Cheminformatics
Library Screening
Repurposing for COVID-19



MD

AP

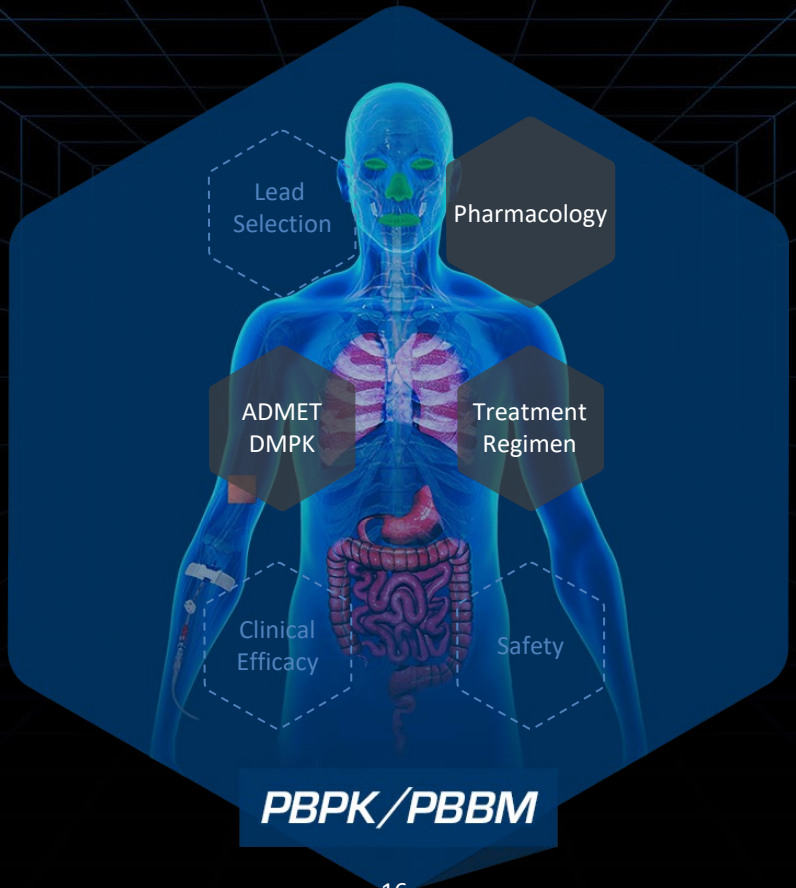
Our *PBPK/PBBM* Solutions Help Address ADMET and DMPK Questions, Touching on Treatment Regimen

Software

GastroPlus®
MembranePlus™
DDDPlus™
ADMET Predictor®

Services

PBPK/PBBM
Preclinical Regulatory Consulting



>70

Approved drug product applications supported by GastroPlus® simulations

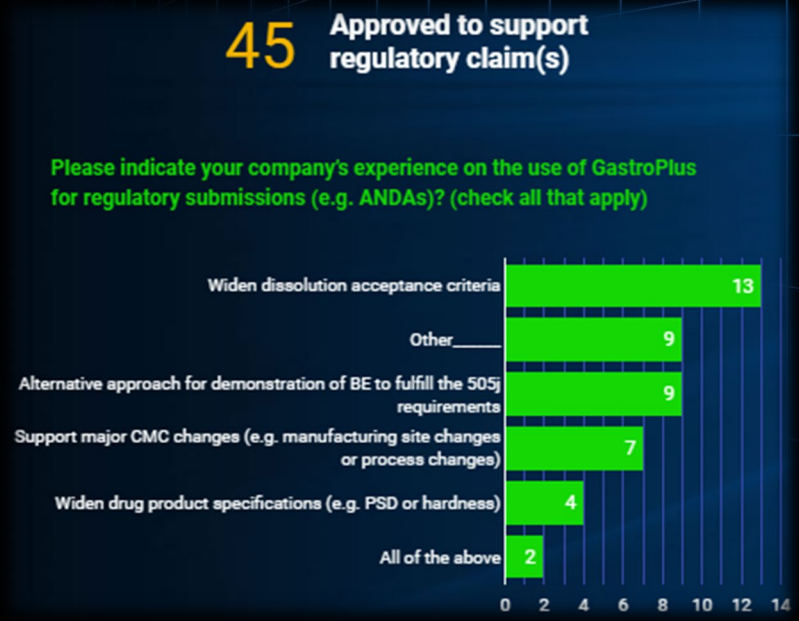
ZURAMPIC

FARYDAK® (panobinostat) capsules 10mg/15mg/20mg

ALECENSA® alectinib 150 mg capsules

Tamiflu® oseltamivir phosphate

Inlyta® axitinib



Manufacturing Process Changes and Virtual Bioequivalence (BE) Trials to Waive Clinical Studies

- Objective: build a PBPK model for an approved drug using existing clinical data for non-engineered formulations (NFE) and perform virtual BE trial simulations vs. the particle engineered (PE) lots to waive the BA/BE study request by the FDA
- Results: baseline model adequately captured existing clinical data and successfully applied to establish product specifications for new PE lots
- Impact: the FDA accepted the modeling results and granted Janssen the BA/BE study request

Tistaert et al. AAPS Annual Conference 2015

Virtual Bioequivalence Study Simulations

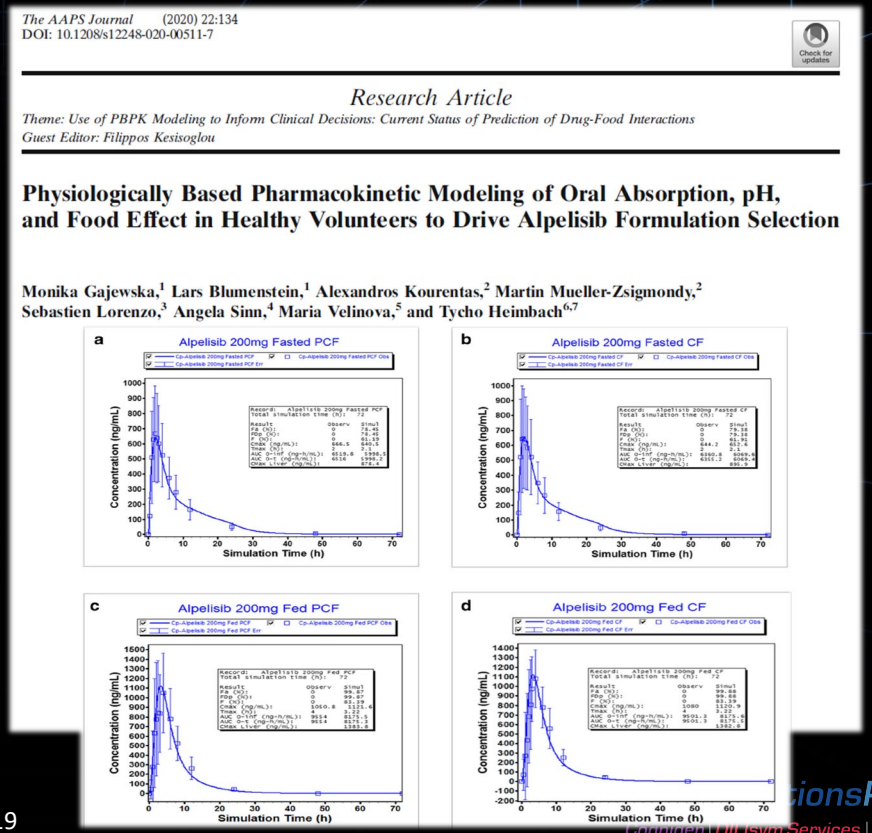
API Lot	PE/NPE	Dose (mg)	AUC_{∞} (ng.h/mL) (N=250)		C_{max} (ng/mL) (N=250)	
			GM	GMR (90% CI)	GM	GMR (90% CI)
Lot 5	PE	50	4180	113.3 (110.7, 116.1)	551	139.3 (136.0, 142.7)
Lot 1	NPE	50	3688		395	
Lot 5	PE	100	8242	103.0 (100.9, 105.1)	551	106.4 (104.3, 108.6)
Lot 3	NPE	100	8001		395	
Lot 5	PE	300	24998	102.2 (99.8, 104.6)	3118	100.0 (97.7, 102.4)
Lot 2	NPE	300	24460		3117	
Lot 5	PE	100	8242	98.2 (96.2, 100.2)	1068	95.1 (93.2, 97.0)
Lot 4	NPE	100	8395		1123	
Lot 5	PE	300	24998	101.9 (99.8, 104.1)	3118	98.3 (96.3, 100.4)
Lot 4	NPE	300	24525		3171	

API: active pharmaceutical ingredient; AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered

PBPK Modeling of pH-Dependent DDIs and Meal Types on Alpelisib (PIQRAY®)

- Objective: develop and verify PBPK model to predict the impact of different meal types and co-administration with pH modifiers on alpelisib (PIQRAY®)
  - Simulation strategy presented outlining evaluation of pivotal clinical formulation (PCF) vs. commercial formulation (CF) under different conditions
- Results: model successfully captures dosing with food and outcome of clinical bioequivalence (BE) studies
- Impact: model results submitted with NDA; serves as foundation for future BE evaluations/pH-mediated DDI assessments and supports drug labeling

Gajewska et al. AAPS J. 2020



The AAPS Journal (2020) 22:134
DOI: 10.1208/s12248-020-00511-7

Research Article

Theme: Use of PBPK Modeling to Inform Clinical Decisions: Current Status of Prediction of Drug-Food Interactions
Guest Editor: Filippos Kesisoglou

Physiologically Based Pharmacokinetic Modeling of Oral Absorption, pH, and Food Effect in Healthy Volunteers to Drive Alpelisib Formulation Selection

Monika Gajewska,[1] Lars Blumenstein,[1] Alexandros Kourentas,[2] Martin Mueller-Zsigmondy,[2] Sebastien Lorenzo,[3] Angela Sinn,[4] Maria Velinova,[5] and Tycho Heimbach[6,7]

Establish Dissolution Safe Space in Adult and Pediatric Populations (TAMIFLU®)

- Objective: develop and verify PBPK model to predict the exposure of oseltamivir (TAMIFLU®) and its main metabolite in adult and pediatric populations
- Results: model successfully captures active and metabolite exposure across population groups and defines dissolution safe spaces unique to each one
- Impact: previous model supported dose selection and trial design in pediatrics; optimized model supports future manufacturing site/formulation changes and sets clinically relevant safe spaces in both adults and pediatrics

The AAPS Journal (2020) 22:107
DOI: 10.1208/s12248-020-00493-6

Check for updates

Research Article

Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations

Lei Miao,[1] Youssef M. Mousa,[1] Liang Zhao,[1] Kimberly Raines,[2] Paul Seo,[2] and Fang Wu[1,3]

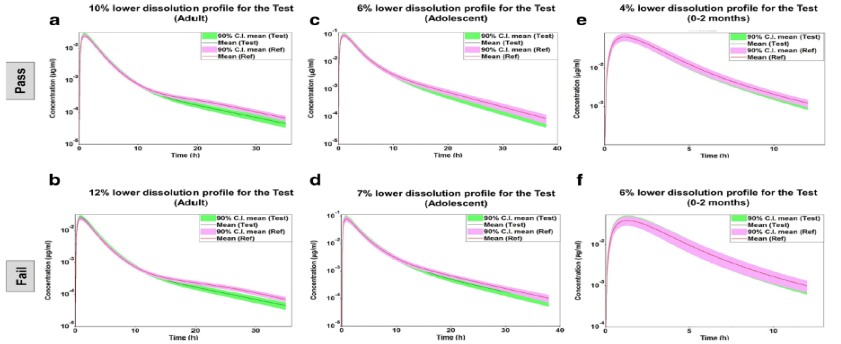


Fig. 4. Virtual BE simulation and analysis for the reference and generic OP products with lower dissolution profiles. **a**, **b** The virtual BE analysis in adults ($n = 50$ subjects) shows that lowering the dissolution profile by 10% is the BE safe space limit to maintain the BE with the reference OP product (**a**). However, lowering the dissolution profile by 12% fails to keep BE with the reference OP product (**b**). **c**, **d** The virtual BE analysis in adolescent (9–18 years, $n = 25$ subjects) shows that lowering the dissolution profile by 6% is the BE safe space limit to maintain the BE with the reference OP product (**c**). However, lowering the dissolution profile by 7% fails to keep BE with the reference OP product (**d**). **e**, **f** The virtual BE analysis in neonates (0–2 months, $n = 25$ subjects) shows that lowering the dissolution profile by 4% is the BE safe space limit to maintain the BE with the reference OP product (**e**). However, lowering the dissolution profile by 6% fails to keep BE with the reference OP product (**f**)

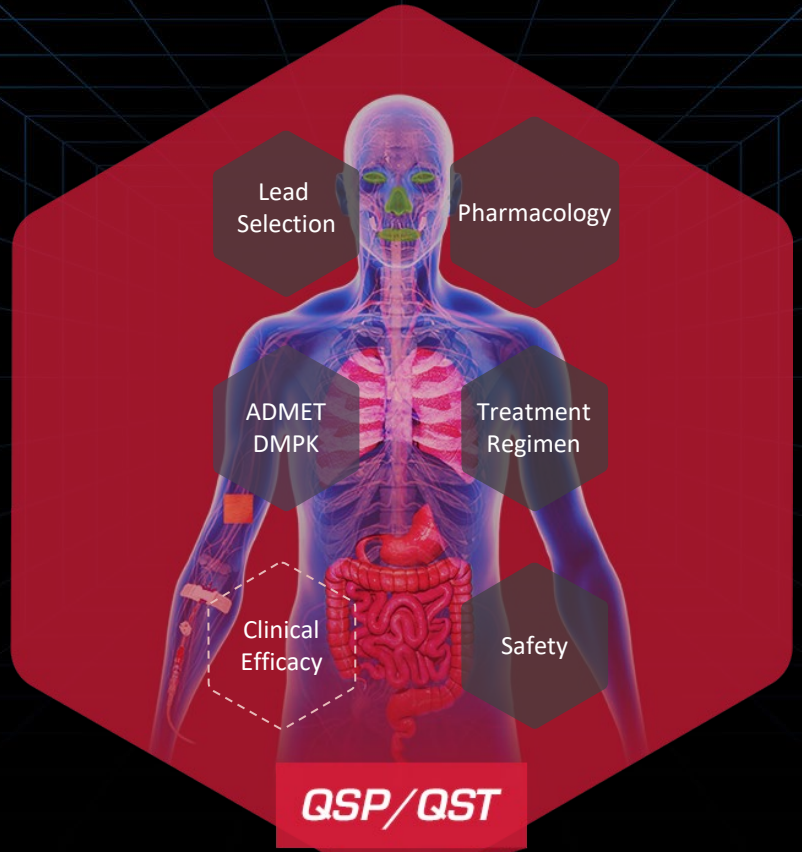
Miao et al. AAPS J. 2020

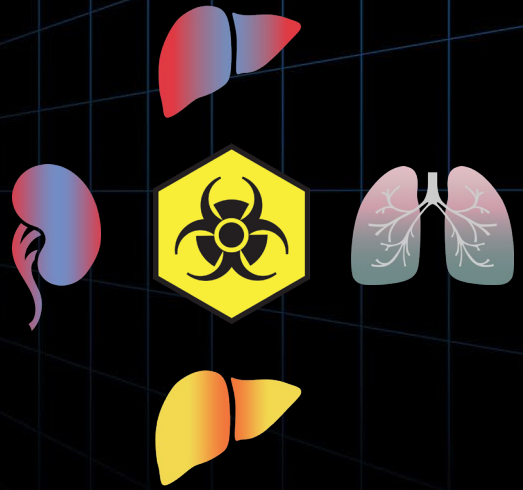
Our *QSP/QST* Solutions Employ Comprehensive, Mechanistic Models to Address Key Drug Development Areas

DILIsym®
RENAsym®
NAFLDsym®
IPFsym™
RADAsym™

Services

QSP Consulting
QST Consulting





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Collaboration with Genentech Focused on Anti-FGFR1/KLB Antibody – Helped Them Determine the Mechanisms Responsible for a Drug Effect

Mathematical Modeling with NAFLDsym Supports the Role of Adiponectin in the Reduction of Steatosis by the Anti-FGFR1/KLB Bispecific Antibody

Zackary R. Kenz[1], Brett A. Howell[1], Ajit Dash[2], Chin Wong[2], Felix L. Yeh[2*], Leslie W. Chinn[2**], Puneet Arora[2**], Kenta Yoshida[2], and Scott Q. Siler[1]

[1]DILIsym Services Inc., Research Triangle Park, NC USA; [2]Genentech, 1 DNA Way, South San Francisco, CA 94080;

Current affiliations: *Alector, 131 Oyster Point Bvld, South San Francisco, CA 94080; **Principia Biopharma, 220 E Grand Ave, South San Francisco, CA 94080

ABSTRACT

The agonist anti-FGFR1/KLB bispecific antibody, BFKB8488A, has been shown to be effective at reducing liver fat in NAFLD patients in a Ph1b study [1]. However, FGFR1/KLB receptors are primarily expressed in adipose rather than liver, suggesting a role for adipokine mediators such as adiponectin (Adpn). Adpn levels have been shown to increase with BFKB8488A treatment. NAFLDsym, a QSP mechanistic, mathematical model of NAFLD and NASH, was employed to evaluate the plausibility of Adpn increases mediating the reduction in liver fat observed with BFKB8488A treatment.

Exposure of BFKB8488A was predicted from PopPK modeling and combined with a mechanistic representation of the effects of BFKB8488A interaction with the FGFR1/KLB complex in adipose. The mechanistic model incorporated the effects of increased Adpn to elicit changes in several hepatic pathways that can act in concert to reduce the hepatic lipid burden. This included decreases in hepatic de novo lipogenesis and mono-acyl glycerol transferase activity along with an increase in hepatic fatty acid oxidation. Subcutaneous administration of 50 mg Q2W, 75 mg Q2W, 100 Q2W or 250 Q4W BFKB8488A was simulated for 12 weeks in a virtual cohort of NAFLD patients with steatosis (n=42).

Generally, simulations of BFKB8488A-mediated increases in Adpn were able to predict comparable reduction in liver fat as those observed in the Ph1b study. Simulated BFKB8488A administration was predicted to increase serum Adpn 40-80% over 12 weeks of dosing in an exposure-related manner (Figure 1), which was within range of the clinical data (except for 100 mg Q2W). Liver fat reductions were predicted to increase in magnitude with increasing dose within the simulated patient population, ranging from 0% to >90% relative to baseline. The inter-patient variability in the liver fat reduction was reasonably predicted. Alternative simulations without Adpn increase did not predict any effects on liver fat.

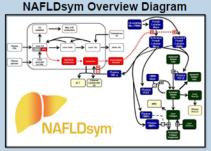
The hypothesis that BFKB8488A-induced increases in Adpn mediate the observed effects on liver fat in NAFLD patients is consistent with NAFLDsym simulations. The similarity between the clinical observations and model predictions utilizing the simulated mechanistic effects of Adpn on hepatic lipid pathways suggests that Adpn participates in mediating the potentially beneficial response to BFKB8488A.

INTRODUCTION

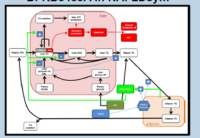
- BFKB8488A, an agonist anti-FGFR1/KLB bispecific antibody, has been shown to be effective at reducing liver fat in NAFLD patients in a Ph1b study (Kunder et al., AASLD 2019)
- FGFR1/KLB receptors are primarily expressed in adipose rather than liver, suggesting a role for adipokine mediators such as adiponectin (Adpn). Adpn levels have been shown to increase with BFKB8488A treatment
- NAFLDsym, a QSP model of NAFLD pathophysiology, was employed to evaluate the plausibility of Adpn increases mediating the reduction in liver fat observed with BFKB8488A treatment

RESULTS

NAFLDsym Overview Diagram



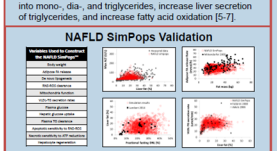
Representation and Optimization of BFKB8488A in NAFLDsym



Description

- BFKB8488A agonist anti-FGFR1/KLB acts on adipose tissue to increase adiponectin secretion from the adipose and increase uptake of triglycerides from the plasma to the adipose. These PD effects were included in the simulations
- The simulations also downstream effects in the liver mediated by changes in the adiponectin receptor which stimulates AMPK [2-4]; these changes decrease de novo lipogenesis, decrease processing of saturated fatty acids into mono-, dia-, and triglycerides, increase liver secretion of triglycerides, and increase fatty acid oxidation [5-7].

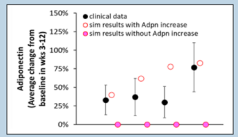
NAFLD SimPops Validation



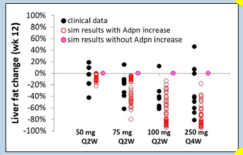
Construction and validation of NAFLD SimPops

- Simulated NAFLD patients (n=1707) include combinations of parameter ranges based on reported responses from literature [8-12].
- Simulated patients within SimPops have pathophysiologic and clinical characteristics consistent with what has been reported in literature [8-12]

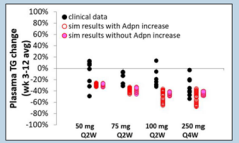
Accurate Prediction of Phase I Clinical Response to BFKB8488A with NAFLDsym



- NAFLDsym accurately predicted (red) clinical responses (black) for adiponectin (Adpn) in representative SimCohorts
- NAFLDsym simulations parameterized without Adpn increase (pink) did not represent clinical Adpn response



- NAFLDsym accurately predicted (red) clinical responses (black) for liver fat in representative SimCohorts, based on dose-dependent Adpn increases mediating liver effects
- NAFLDsym simulations parameterized without Adpn increase (pink) did not represent clinical liver fat response



- NAFLDsym reasonably predicted (red) the clinical responses (black) for plasma TG changes in representative SimCohorts, accounting for wide clinical variability in plasma TG responses

METHODS

Overview NAFLDsym is a mechanistic, mathematical QSP model that was utilized for all simulations. NAFLDsym includes a representation of the primary pathways controlling liver fatty acid and triglyceride fluxes in addition to the effects of lipotoxicity on hepatocellular health. NAFLDsym v2A also contains submodels describing the pathophysiology of inflammation and fibrosis; these submodels were not the focus for the simulations described herein. The primary simulated NAFLDsym outputs utilized were adiponectin, ALT, liver fat, and plasma TG.

Simulated patients A simulated population of patients with the pathophysiological aspects of NAFLD are included in NAFLDsym. This SimPops (n=1707) includes a number of characteristics that are consistent with the observed heterogeneity of pathophysiologic and clinical features of NAFLD. For this study, a subset of all simulated patients (SimCohorts, n=42) with similar characteristics as the clinical cohort was utilized.

Simulated effects of BFKB8488A High molecular weight (HMW) adiponectin has been shown to increase the activity of hepatocellular AMPK following its interaction with the ADIPO R1 and R2 receptors [2-4]. In separate studies employing pharmacologic activators of AMPK in hepatocytes or HepG2 cells, AMPK activity has been demonstrated to reduce the expression and/or activity of ACC and FAS [5]. These are rate controlling enzymes of the de novo lipogenesis (DNL) pathway; reductions in expression/activity of these enzymes reduce flux through the DNL pathway. ACC also regulates the entry of fatty acids into the mitochondria; reduced ACC activity allows for greater fatty acid entry into the mitochondria to support fatty acid oxidation [6]. Additional studies have shown that AMPK activation reduces the hepatocellular expression/activity of MGAT, one of the enzymes that participates in the esterification of fatty acids to triglycerides [7]. Exposure-response relationships between HMW adiponectin and DNL inhibition, enhanced fatty acid oxidation, enhanced VLDL-TG secretion, and inhibition of fatty acid esterification, respectively were included within NAFLDsym v2A.

A subset of Genentech's ANTI-FGFR1/KLB MAB Phase Ib clinical data (50 mg Q2W and 250 mg Q4W) were used to optimize the quantitative relationships of each effect; the quantitative relationships based on the in vitro studies [5], [7] were not employed due to uncertainty of translating the quantitative aspects to humans. Validation of the optimized quantitative effects on DNL inhibition, fatty acid oxidation, and MGAT inhibition was performed by comparing simulation results with additional Phase Ib clinical data (75 mg Q2W and 100 mg Q2W).

Simulations were also conducted without parameterizing an adiponectin increase, to test the key method of action hypothesis for BFKB8488A.

Simulated Protocols Subcutaneous administration of 50 mg Q2W, 75 mg Q2W, 100 Q2W or 250 Q4W BFKB8488A was simulated for 12 weeks in a virtual cohort of NAFLD patients with steatosis

CONCLUSIONS

NAFLDsym simulated predictions of 12 weeks of treatment with the agonist anti-FGFR1/KLB bispecific antibody BFKB8488A indicate that:

- BFKB8488A administration was predicted to increase serum Adpn 40-80% over 12 weeks of dosing in an exposure-related manner, within the clinical data range
- Liver fat reductions in the simulated patients were predicted to increase in magnitude with increasing dose, and simulated magnitudes were consistent with the observed liver fat reduction
- Simulations parameterized without an adiponectin

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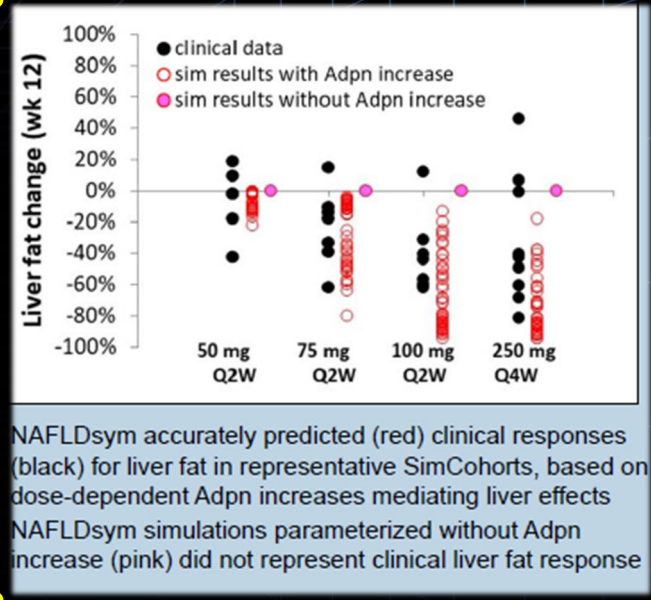

NAFLDsym accurately predicted (red) clinical responses (black) for liver fat in representative SimCohorts, based on dose-dependent Adpn increases mediating liver effects

NAFLDsym simulations parameterized without Adpn increase (pink) did not represent clinical liver fat response

Important DILIsym Application Examples

Pharm Res (2020) 37:24
https://doi.org/10.1007/s11095-019-2726-0

Check for updates

RESEARCH PAPER

Comparison of the Hepatotoxic Potential of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease Using Quantitative Systems Toxicology Modeling

J. L. Woodhead[1] • L. Pellegrini[2] • L. K. M. Shoda[1] • B. A. Howell[1]

Table 7 Comparison between simulation and clinical results for lixivaptan from this study and for tolvaptan from previously published research (9) at the maximum intended doses for ADPKD

Drug	Dose	Duration	Parameter Settings	Simulated ALT >3X ULN*	Clinical ALT >3X ULN	Simulated Hy's Law Cases	Clinical Hy's Law Cases
Lixivaptan	200/100 mg	12 weeks	Default measured#	0/285 (0.0%)	Study not yet conducted	No	Study not yet conducted
Tolvaptan	90/30 mg	24 weeks	Default measured#	18/229 (7.86%)	4.4% and 5.6%	Yes	Yes

*Upper limit of normal (ULN) in DILIsym is 40 U/L

#Default lixivaptan assumption for BA inhibition is mixed inhibition type with $\alpha = 5$ in the absence of K_i studies, based on the authors' experience

Analyzing the Mechanisms Behind Macrolide Antibiotic-Induced Liver Injury Using Quantitative Systems Toxicology Modeling

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Received: 24 September 2018 / Accepted: 27 January 2019 / Published online: 7 February 2019

ABSTRACT
Purpose Macrolide antibiotics are commonly prescribed treatments for drug-resistant bacterial infections; however

Conclusions The mechanisms responsible for toxicity can be significantly different within a class of drugs, despite the structural similarity among the drugs. QST modeling can provide

84-93

Mechanistic Investigations Support Liver Safety of Ubrogepant

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Assessment of the Mechanism for Remdesivir-Associated Clinical ALT Elevations Using DILIsym Quantitative Systems Toxicology Modeling

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- Remdesivir, a monophosphoramidate prodrug of a nucleoside analog, has been granted Emergency Use Authorization in the U.S. for the treatment of hospitalized COVID-19 patients.
- In a Ph1 clinical study in healthy volunteers treated with the 150 mg daily dose of remdesivir for 7 or 14 days (higher than the current clinical dose) [1], reversible low- grade elevations of serum ALT and AST were observed at 5-25 days after the first dose in 8 out of 16 individuals.

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IV Remdesivir 150 mg Single Dose

The PBPK

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Compound	Mechanism	Parameter	Unit	Value*
Remdesivir	Bile Acid Transport Inhibition	Inhibition constant (IC_{50}) for BSEP	µM	22
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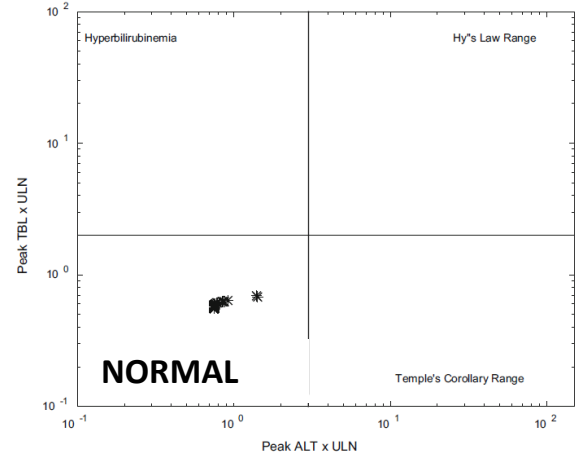
Phosphorylated metabolites[1]	Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	µM	4203

DILIsym parameter values identified from *in vitro* mechanistic toxicity data.

* Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to

Fig. 6 eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plot showing DILIsym simulated liver safety outcomes for 200/100 mg split daily dosing of lixivaptan over 12 weeks in the lixivaptan-specific SimPops of 285 simulated normal healthy volunteers including lixivaptan PK variability.



Important DILIsym Application Examples

Pharm Res (2020) 37:24
https://doi.org/10.1007/s11095-019-2726-0

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RESEARCH PAPER

Comparison of the Hepatotoxic Potential of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease

Pharm Res (2019) 36: 48
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Table V Most Likely Mechanism of Toxicity Suggested by the Simulation Results for Each Macrolide Antibiotic

DILI mechanism	Solithromycin	Clarithromycin	Erythromycin	Telithromycin	Azithromycin
Mitochondrial dysfunction	**Predominant**	**Predominant**	None	None	Plausible
Oxidative stress	None	None	Minor	None	None
Bile acid transporter inhibition	Minor	Minor	**Predominant**	Plausible	None
Mechanism not included in DILIsym	Unlikely	Unlikely	Unlikely	**Plausible**	**Plausible**

The mechanism suggested by DILIsym as the most likely to contribute to the observed toxicity is rendered in bold

Mechanistic Investigations Support Liver Safety of Ubrogepant

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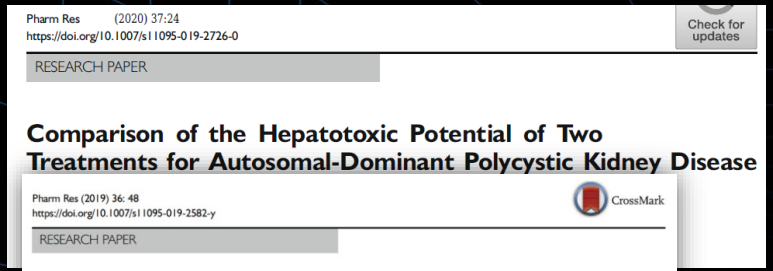
Important DILIsym Application Examples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TOXICOLOGICAL SCIENCES, 177(1), 2020, 84–93

doi: 10.1093/toxsci/kfaa093
Advance Access Publication Date: 24 June 2020
Research Article

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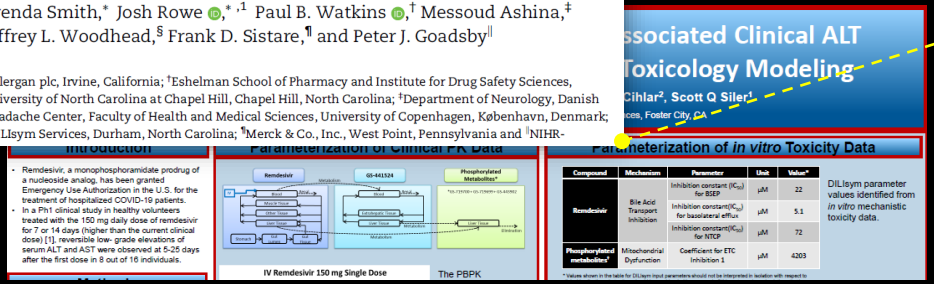
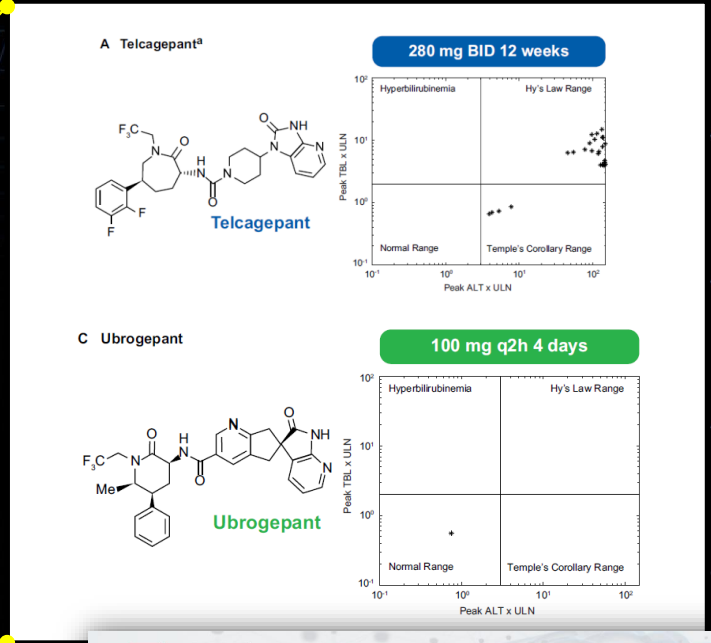
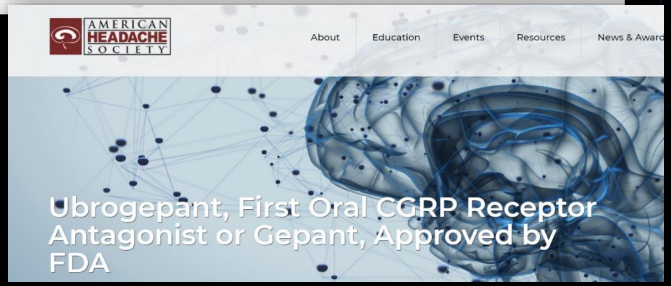
Brenda Smith,* Josh Rowe,*,[1] Paul B. Watkins,† Messoud Ashina,‡ Jeffrey L. Woodhead,§ Frank D. Sistare,¶ and Peter J. Goadsby‖

*Allergan plc, Irvine, California; †Eshelman School of Pharmacy and Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ‡Department of Neurology, Danish Headache Center, Faculty of Health and Medical Sciences, University of Copenhagen, København, Denmark; §DILIsym Services, Durham, North Carolina; ¶Merck & Co., Inc., West Point, Pennsylvania and ‖NIHR-







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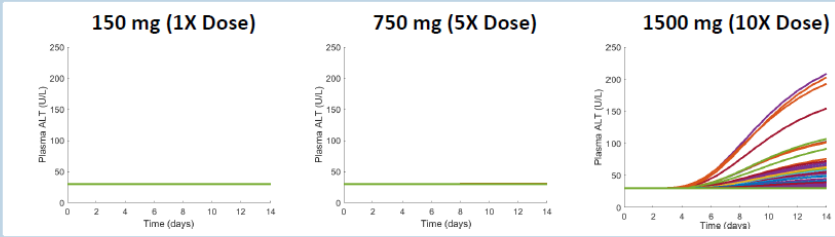
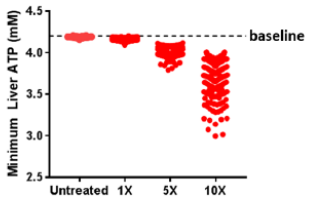
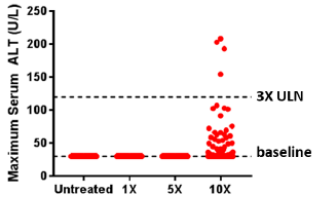
Simulated Hepatic Biomarkers in SimPops (n=300) administered remdesivir







Conclusions

- Clinically-observed reversible low-grade ALT increases following multiple dose treatment with 150 mg of remdesivir for 7 or 14 days are unlikely to be due to mitochondrial electron transport chain or bile acid transport inhibition, indicating potentially alternative mechanisms.

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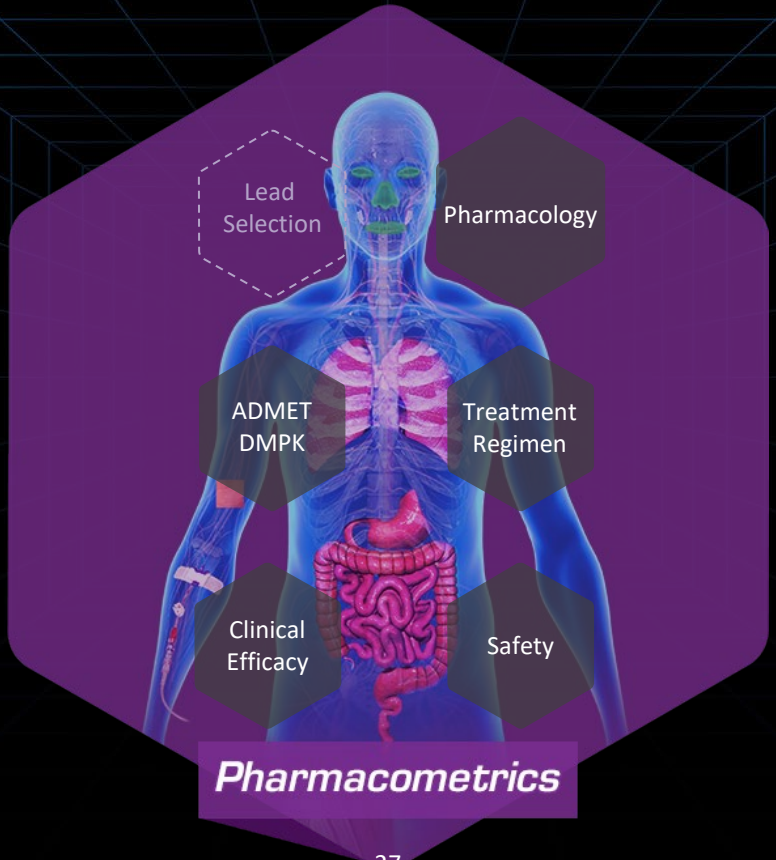
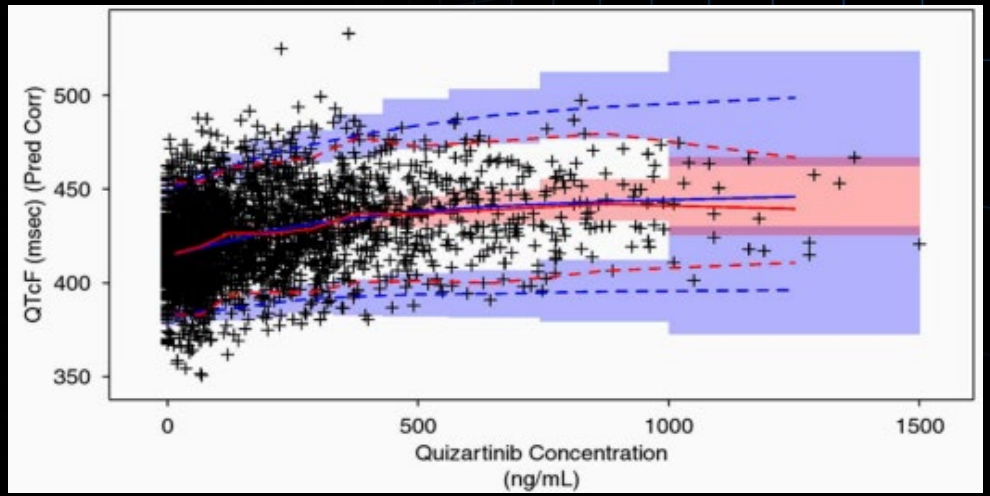


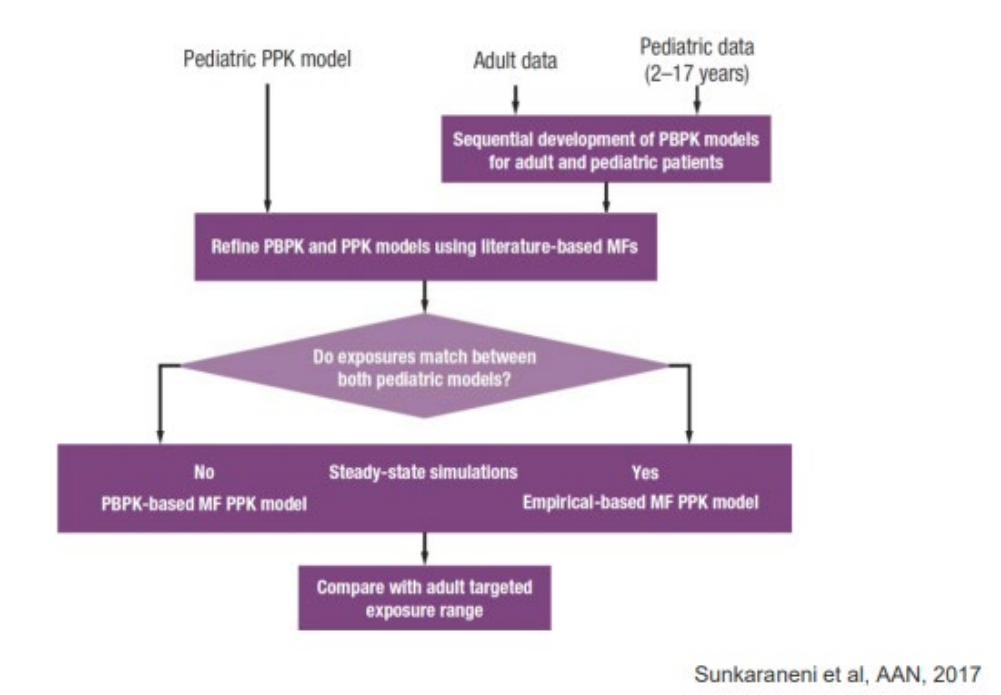
Concentration-QT Model-based Risk Assessment for Quizartinib

- Population PK models of quizartinib and its major metabolite (AC886) identified strong CYP3A inhibitor use as a clinically meaningful factor affecting quizartinib PK exposure
- Concentration-QT models predicting the risk of QT prolongation in relation to drug and metabolite exposure were developed to quantify risk with alternative dosing regimens and support labelling recommendations
- Results helped to quantify risk associated with QT prolongation and supported dose reduction in patients receiving strong CYP 3A inhibitors

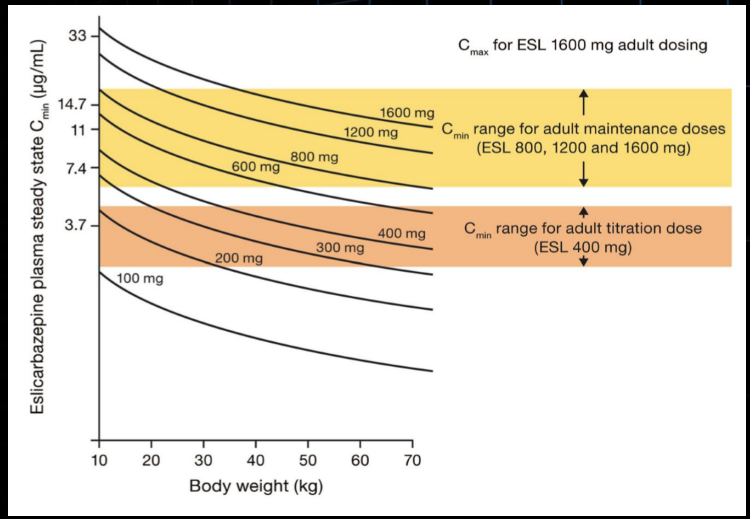


Comparison of PK and QTc Effect of Quizartinib in Japanese and non-Japanese Patients with Relapsed/Refractory FLT3-ITD+ AML using PopPK Analyses, Nakayama S et al. Poster presented at ACoP 2020.

Pediatric Dose Selection: Value of Alternative Modeling Approaches, PBPK and Population PK



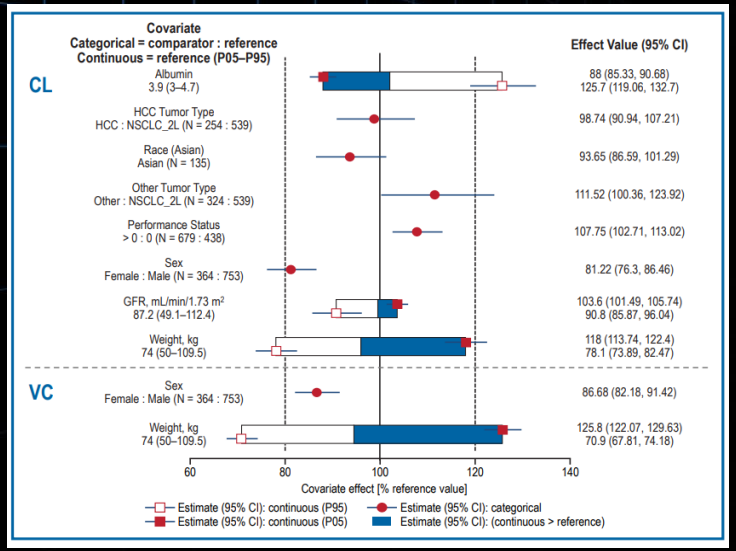
Complementary PBPK and population PK modeling approaches used to increase confidence in selection of eslicarbazepine acetate dosing regimen for further evaluation in children with partial-onset seizures aged 1 - <24 months

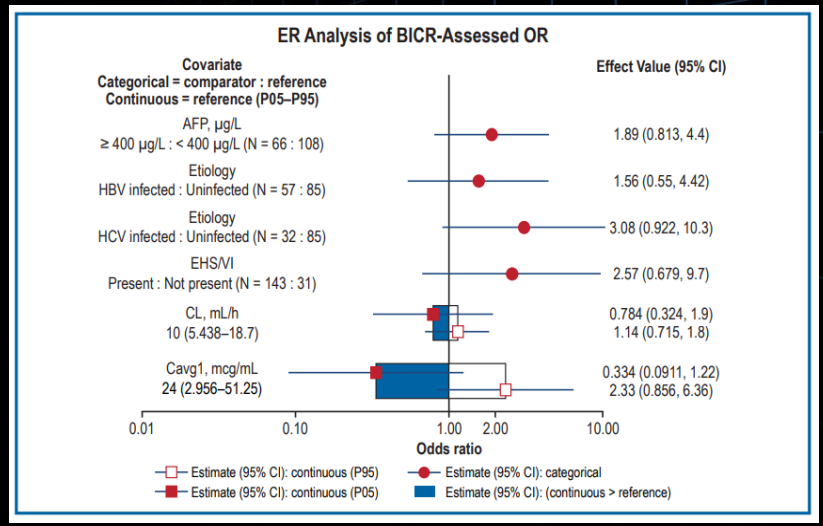


PBPK and PopPK M&S to Support Dose Selection and Study Design for Eslicarbazepine acetate Adjunctive Therapy in Infants with POS. Sunkaraneni et al, Poster presented at AAN, 2017.
M&S to Support Dose Selection for Eslicarbazepine acetate Therapy in Pediatric Patients with POS. Sunkaraneni et al., JPKPD 45 (2018).

Model-informed Approaches to Characterize Exposure-Response and Determinants of Safety and Efficacy

- Population PK modeling has been used to characterize time-varying CL and the impact of various intrinsic factors on the PK of nivolumab, a fully human IgG4 approved for the treatment of multiple cancer types in the US and other countries
- E-R models were developed to predict overall response based on RECIST criteria and the impact of various factors on E-R; knowledge of E-R relationships supported clinical pharmacology understanding for the approval of new indications and for dosing regimen selection/labeling





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Population PK and Exposure-Efficacy Analyses of Nivolumab in Patients with Advanced Hepatocellular Carcinoma, Wang X et al. Poster presented at ACoP 2017.

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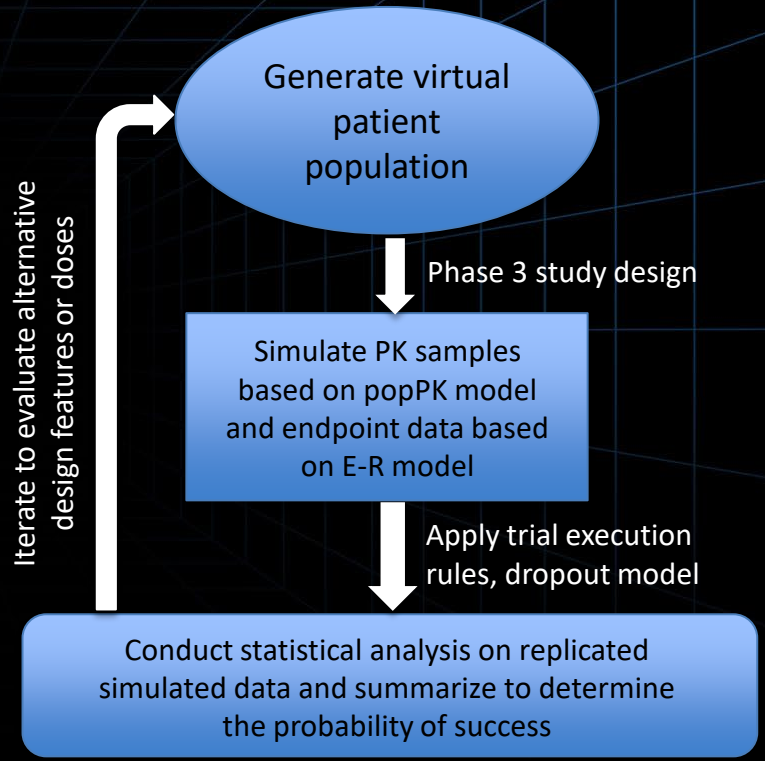
Simulations to Improve the Probability of Phase 3 Success

Timely performance of clinical trial simulations can be used effectively to **increase the probability of Phase 3 success** by **evaluating the impact of various study design features** including:

- appropriate inclusion/exclusion criteria
- optimal sampling for PK and PD to achieve differentiation between placebo and treatment, and
- optimal dose and dosing regimen

to achieve the desired benefit-risk profile.



Q&A

Questions & Answers

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