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OPCO Fireside Chat
December 17, 2020

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With the exception of historical information, the matters discussed in this presentation are forward-looking statements that involve a number of risks and uncertainties. The actual results of the Company could differ significantly from those statements. Factors that could cause or contribute to such differences include but are not limited to: continuing demand for the Company's products, competitive factors, the Company's ability to finance future growth, the Company's ability to produce and market new products in a timely fashion, the Company's ability to continue to attract and retain skilled personnel, and the Company's ability to sustain or improve current levels of productivity. Further information on the Company's risk factors is contained in the Company's quarterly and annual reports and filed with the Securities and Exchange Commission.

Modeling and Simulation in Pharma Drug Development

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.

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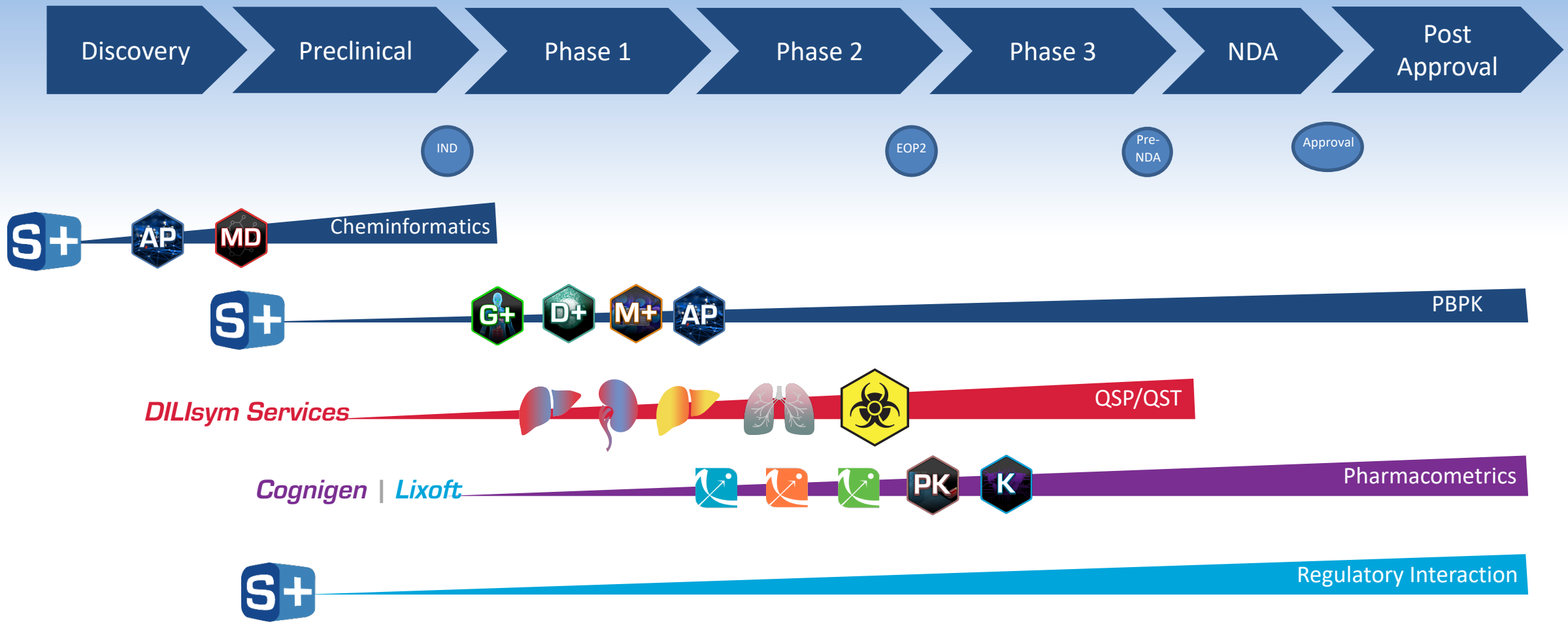
- Synergies come from shared knowledge between client and consultant
- We welcome involvement, participation, and input from stakeholders outside of M&S

Our solutions inform the entire drug development process



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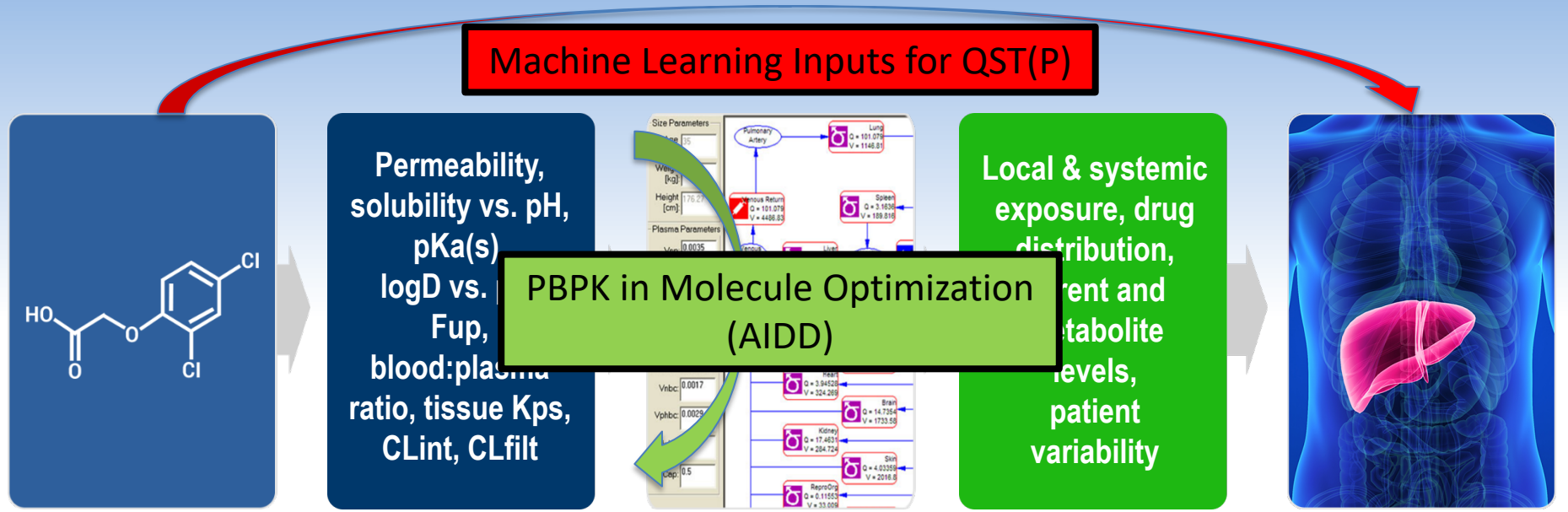
Technology Overview:
The Machine Learning / PBPK / QST(P) Marriage…



ADMET Predictor™

GastroPlus™

RENAsym™ DILIsym® RADAsym™

Next-Gen IVIVE

PKPlus™ DDDPlus™ IPFsym™ NAFLDsym

MembranePlus™

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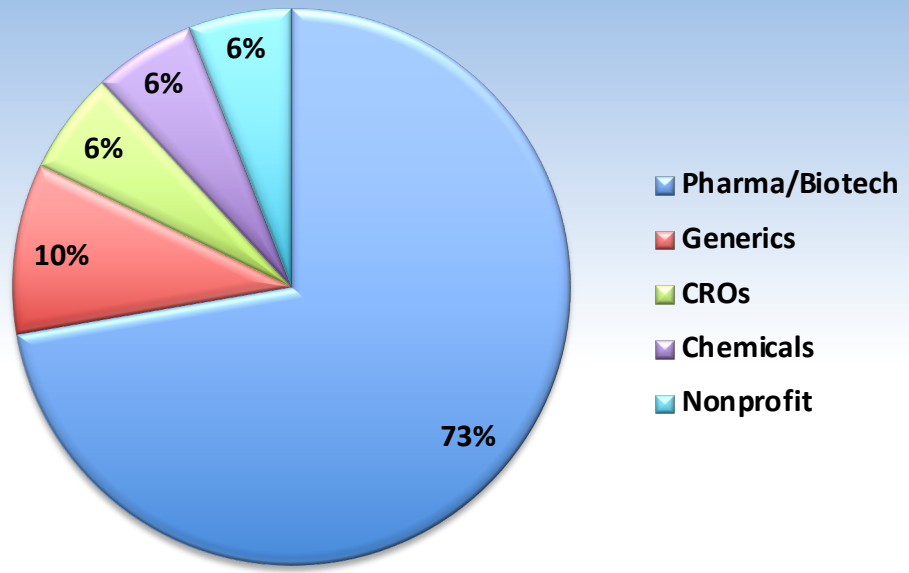
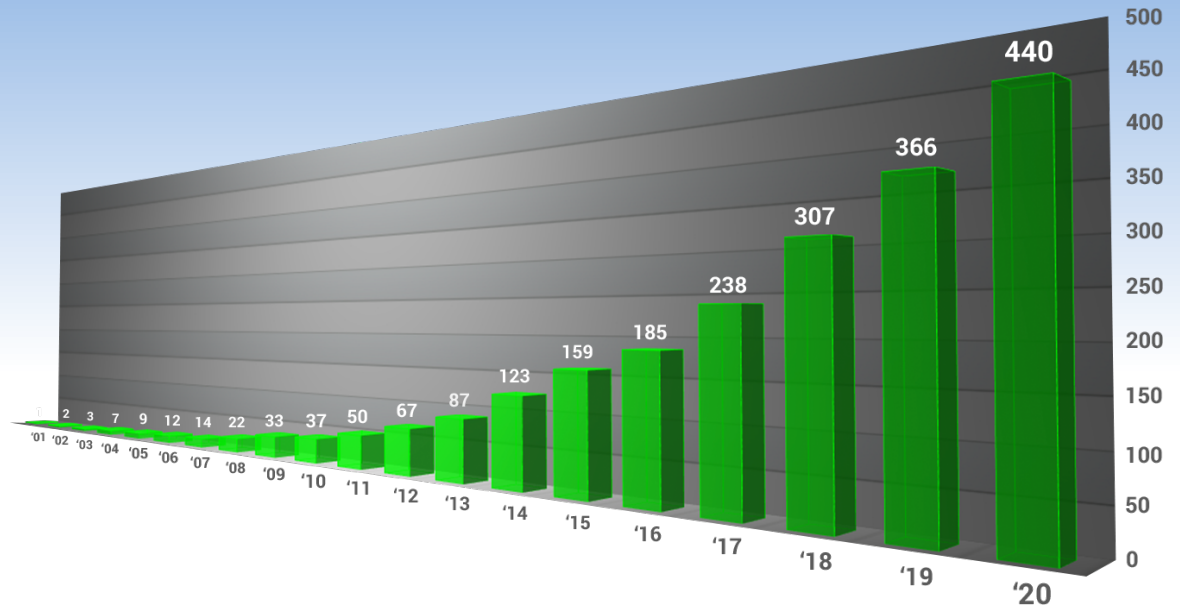
G+: By the numbers…

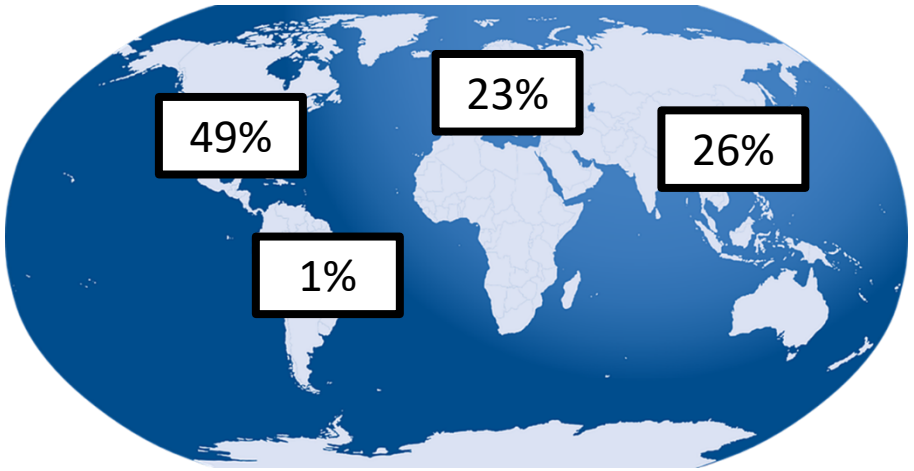
% Revenue by Client Type



Peer-reviewed journal publications



% Revenue by Geography



- GastroPlus® client base: ~160 commercial companies and >90 nonprofit organizations
- >60 commercial companies license $100K+
- All major global regulatory agencies have access and reviewers trained on the platform
- ~93% customer retention rate (fees)

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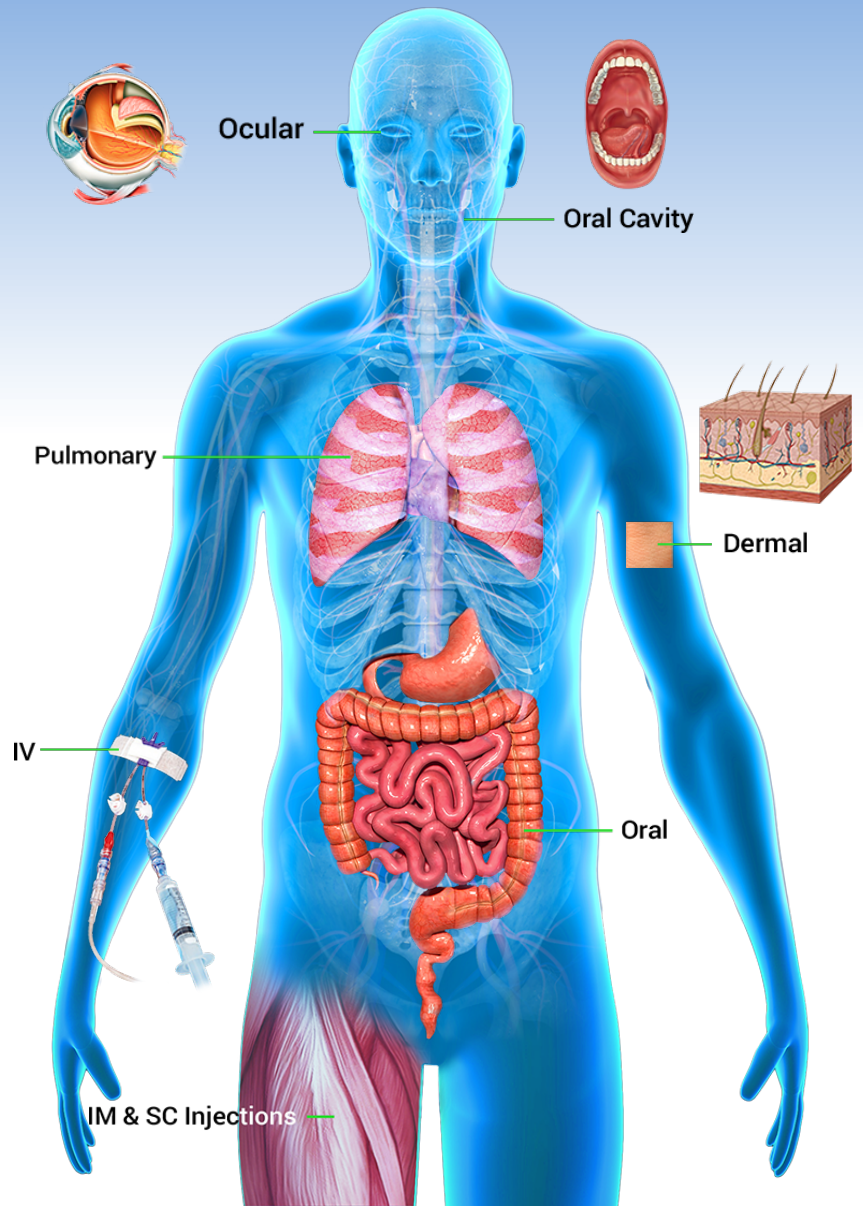
Clients Driving Software R&D: Funded Collaborations



FDA: Ocular model extensions
Est. end date: 4QFY22

FDA: Oral cavity model extensions
Est. end date: 4QFY23

FDA: Dermal model extensions
Est. end date: 4QFY21

Cosmetics Europe: Dermal model extensions
Est. end date: 2QFY21

Large Pharma: Pulmonary model extensions
Est. end date: 2QFY21

Large Pharma: Gut model extensions
Est. end date: 2QFY21

Large Pharma: Virtual BE trial simulator
Est. end date: 2QFY21

Large Pharma: Peptide absorption
Est. end date: 2QFY22

Themes:

- Whole-body mechanistic absorption
- Advanced formulations
- Animal->human translation
- Population simulations
- Virtual BE
- Library screening/optimization
- Peptide administration

>70

Approved drug product applications supported by GastroPlus® simulations

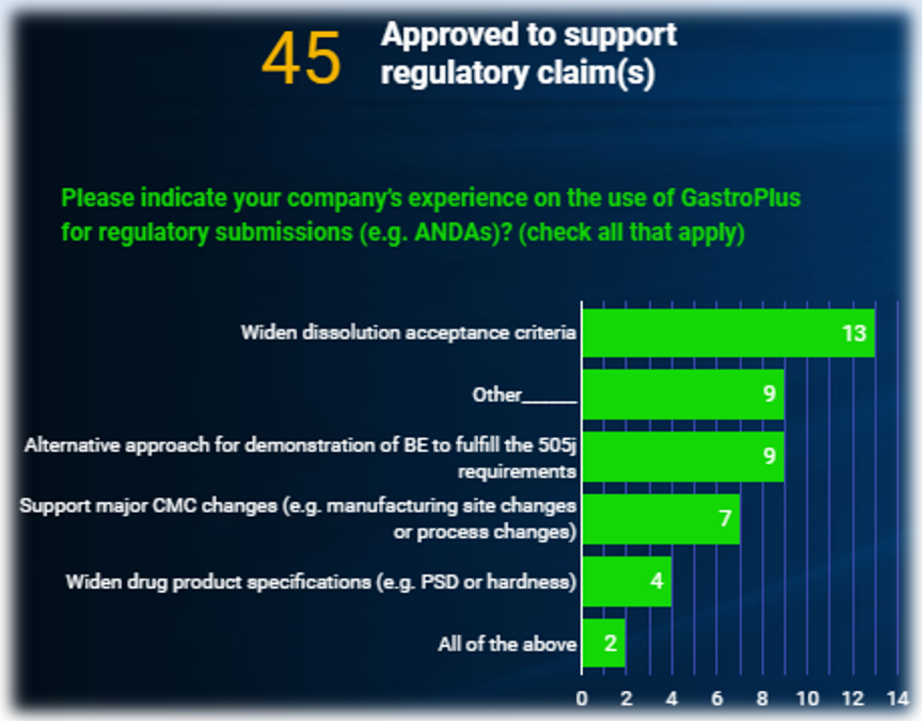
ZURAMPIC

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

ALECENSA™

Tamiflu® oseltamivir phosphate

Inlyta® axitinib



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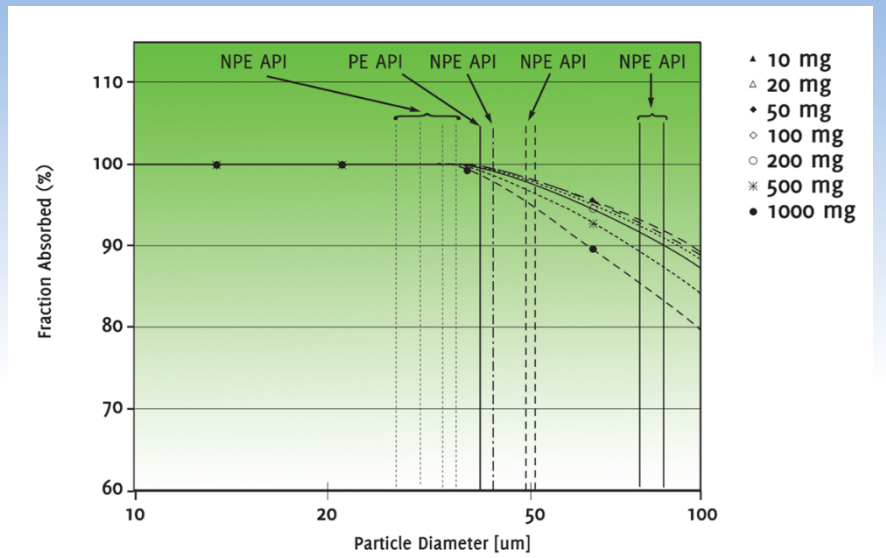
Manufacturing Process Changes and Virtual Bioequivalence (BE) Trials to Waive Clinical Studies

- 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
  - Simulation strategy presented describing the assessment of drug product specifications and virtual BE
- 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



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

Tistaert et al. AAPS Annual Conference 2015

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

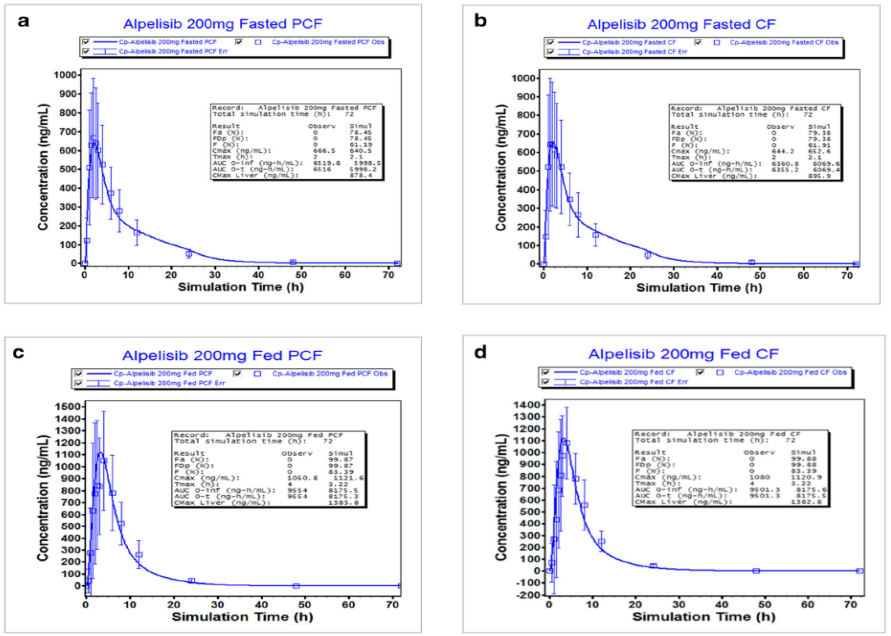
The AAPS Journal (2020) 22:134
DOI: 10.1208/s12248-020-00511-7

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]



Gajewska et al. AAPS J. 2020

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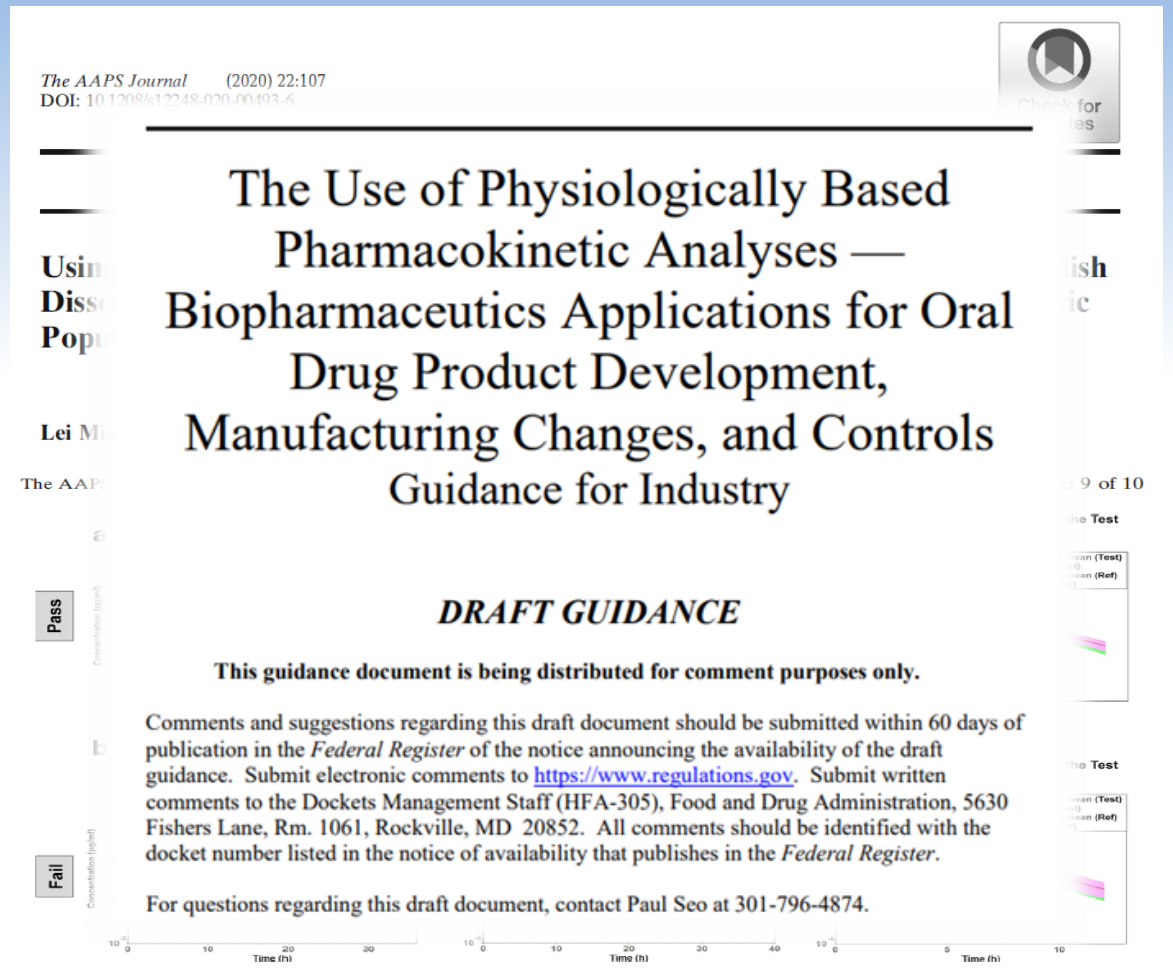
Establish Dissolution Safe Space in Adult and Pediatric Populations (TAMIFLU®)

- Objective: develop and verify PBPK model to predict the exposure of oseltamivir (TAMIFLU®) and its main metabolite in adult and pediatric populations
  - Simulation strategy presented model development in adults and extrapolation to pediatrics at different age groups

- 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

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Paul Seo at 301-796-4874.

Pass
Fail

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

DILIsym Services Inc., an SLP Company

"Our vision is safer, effective, more affordable medicines for patients through modeling and simulation."

- DILIsym Services, Inc. offers comprehensive program services:
  - **DILIsym** software licensing, training, development (consortia)
  - **NAFLDsym** and **IPFsym** software licensing, training, development
  - **QSP / QST** simulation consulting projects
  - Consulting and data interpretation; *in vitro* assay experimental design and management
  - **RENAsym** and **RADAsym** software in development

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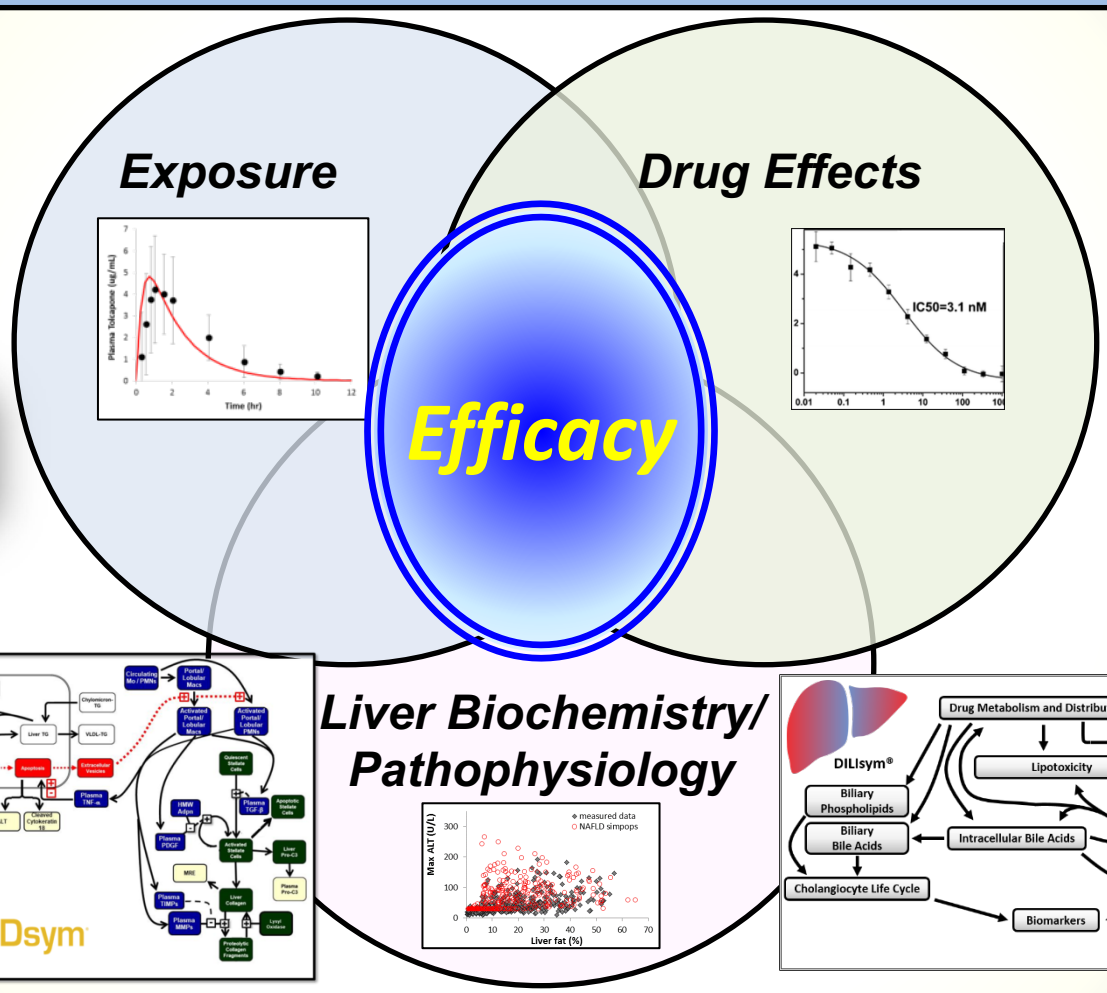
DILIsym Services Is Using QSP and QST Modeling to Predict Efficacy and Safety of Drugs in Development

Predicted compound concentrations at site of target often require PBPK models



PD effects and interactions with underlying biochemistry unique for most compounds; QSP model needs to be flexible to provide ability to represent these effects

Mechanistic representation of underlying biochemistry describing pathophysiology is foundation of QSP models

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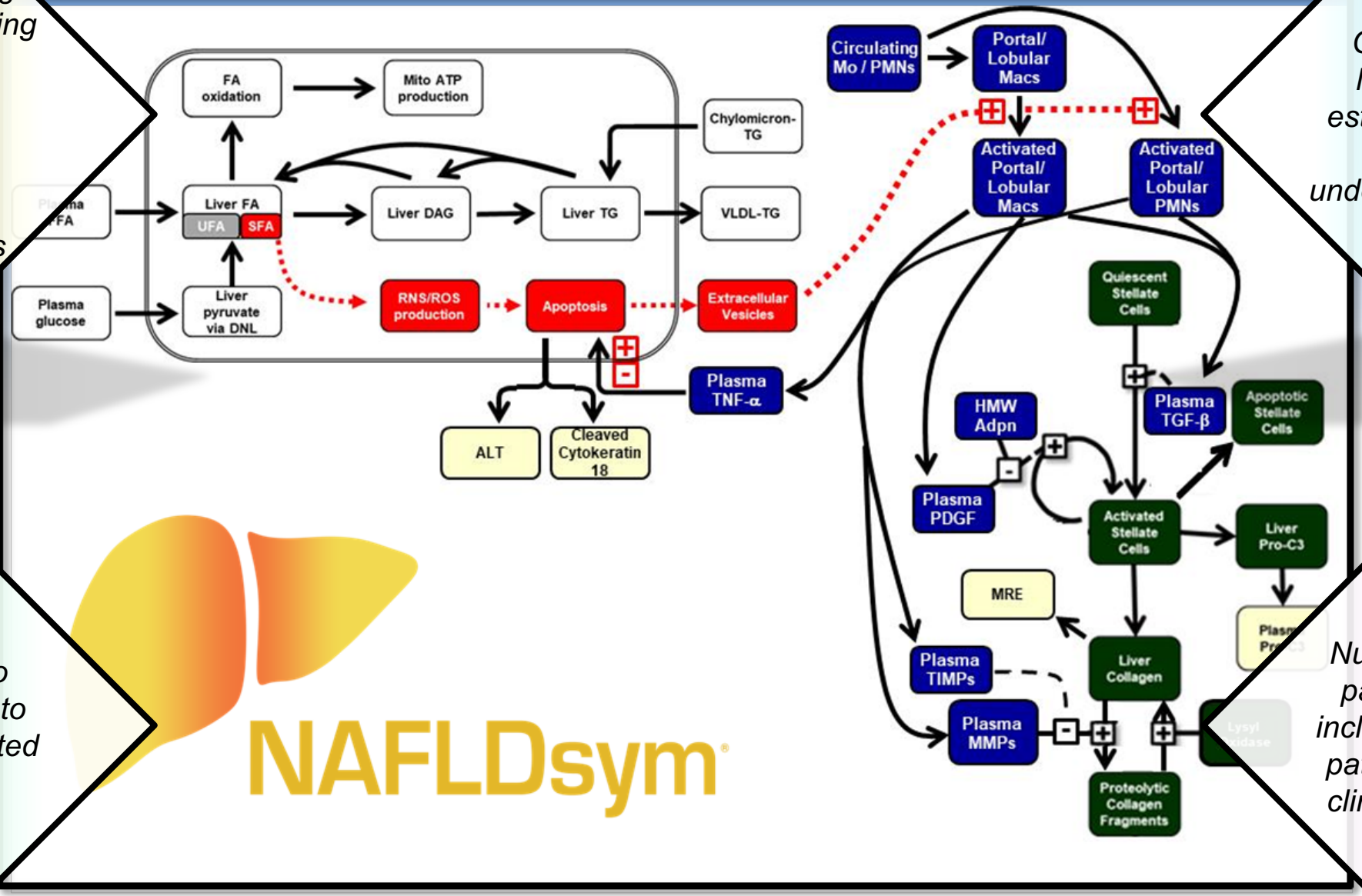
NAFLDsym v2A Overview

Multiple interacting sub-models, including

- *Steatosis*
- *Lipotoxicity*
- *Inflammation*
- *Fibrosis*
- *Biomarkers*
- *Weight gain/loss*

Clinical data from literature used to establish quantitative relationships for underlying biochemistry



Provides ability to predict responses to treatment in simulated clinical trials

Numerous simulated patients (SimPops) included to account for pathophysiologic and clinical heterogeneity

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

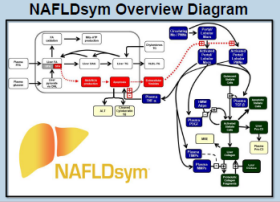
The hypothesis that BFKB8488A-induced increases in Adpn mediate the observed effects on liver fat in NAFLD patients is consistent with NAFLDsym simulations. The similarity between the clinical observations and model predictions utilizing the simulated mechanistic effects of Adpn on hepatic lipid pathways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

INTRODUCTION

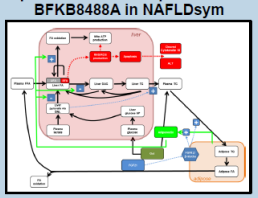
- BFKB8488A, an agonist anti-FGFR1/KLB bispecific antibody, has been shown to be effective at reducing liver fat in NAFLD patients in a Ph1b study (Kunder et al., AASLD 2019)
- FGFR1/KLB receptors are primarily expressed in adipose rather than liver, suggesting a role for adipokine mediators such as 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



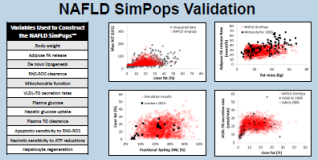
Representation and Optimization of BFKB8488A in NAFLDsym



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].

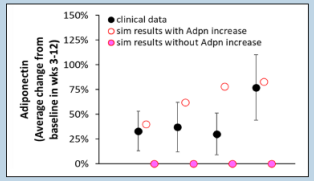
NAFLD SimPops Validation



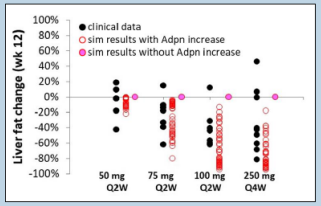
Construction and validation of NAFLD SimPops

- 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]

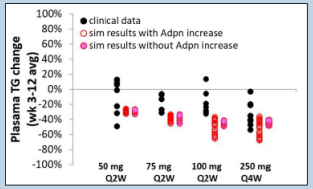
Accurate Prediction of Phase I Clinical Response to BFKB8488A with NAFLDsym



- 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 increase did not represent the clinical response

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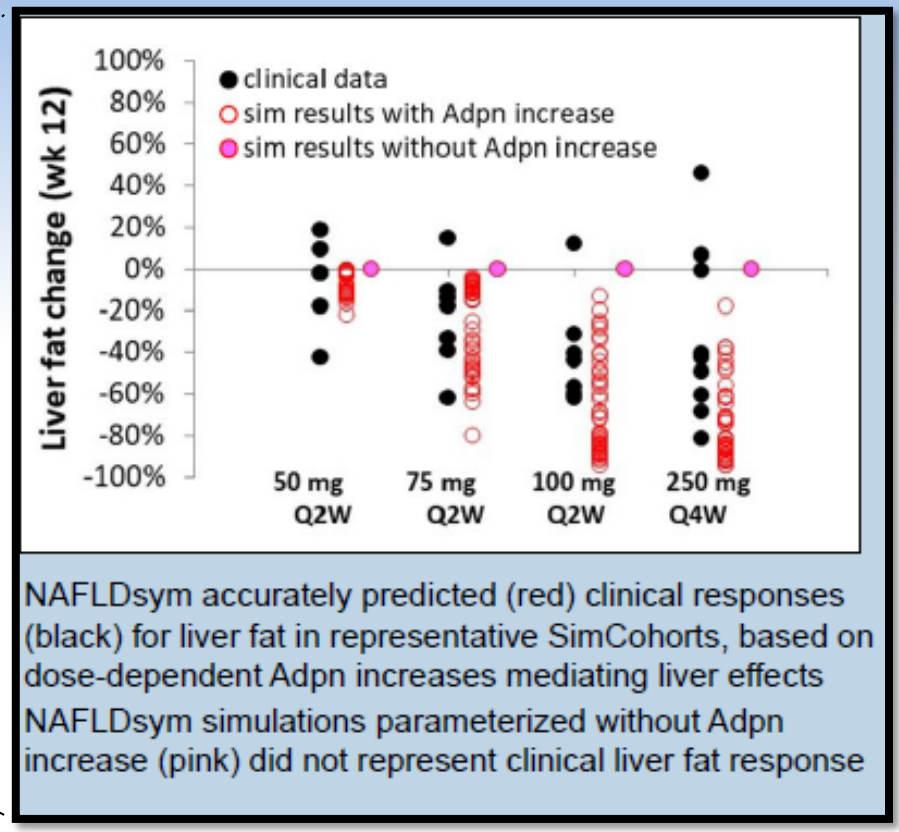

NAFLDsym accurately predicted (red) clinical responses (black) for liver fat in representative SimCohorts, based on dose-dependent Adpn increases mediating liver effects

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

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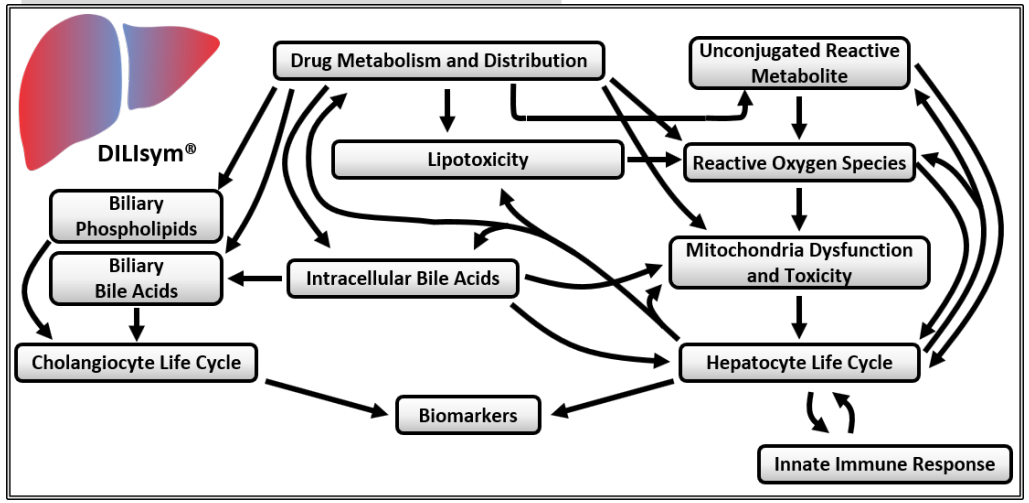
How the DILIsym Software Helps Drug Developers

DILIsym®

- Predicts drug-induced liver disease
- Includes mechanistic representation of normal hepatic biochemistry



So how can DILIsym help my organization?

- Predict DILI liabilities beforehand and save **$$$**
- Choose the lead candidate ***most likely to succeed*** from a DILI standpoint
- Communicate with regulators on safety issues with information they have requested from others numerous times and from a platform they license (FDA)
- ***Keep patients safer….***

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DILIsym Utilizes Various Data Types to Inform Decisions

Exposure Data

PBPK Modeling

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid / phospholipid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP, (MDR3)*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

Modeling & Simulation

Simulations and Assays inform:

- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

Clinical Information

- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

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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 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

Jeffrey L. Woodhead[1] • Kyunghee Yang[1] • David Oldach[2] • Chris MacLauchlin[2] • Prabhavathi Fernandes[2] • Paul B. Watkins[3] • Scott Q. Siler[1] • Brett A. Howell[1]

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

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Mechanistic Investigations Support Liver Safety of Ubrogepant

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Jeff

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

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Introduction

- 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.
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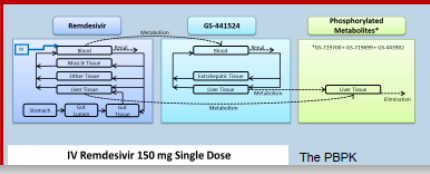

IV Remdesivir 150 mg Single Dose

The PBPK

Parameterization of *in vitro* Toxicity Data

Compound	Mechanism	Parameter	Unit	Value*
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Phosphorylated metabolites*	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.

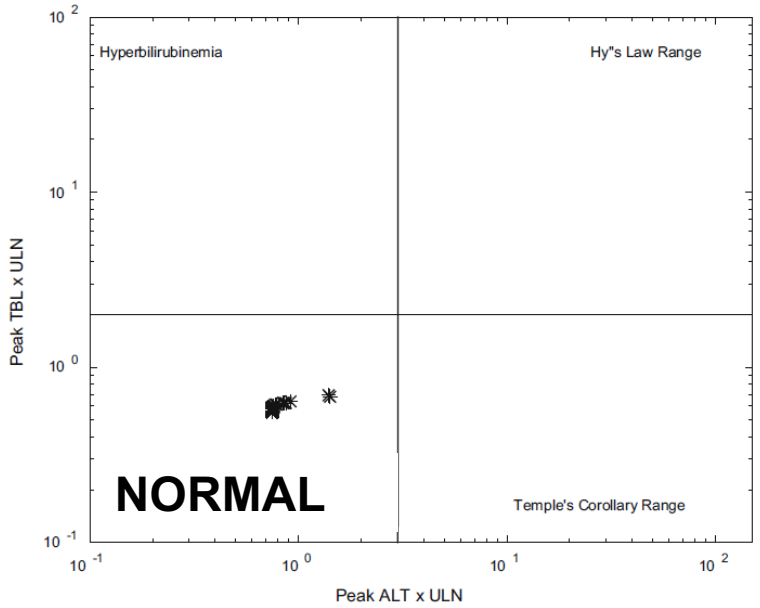

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Table V Most Likely Mechanism of Toxicity Suggested by the Simulation Results for Each Macrolide Antibiotic

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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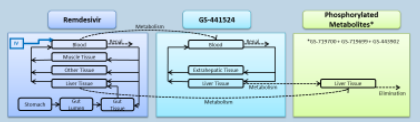

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TOXICOLOGICAL SCIENCES, 177(1), 2020, 84–93

doi: 10.1093/toxsci/kfaa093
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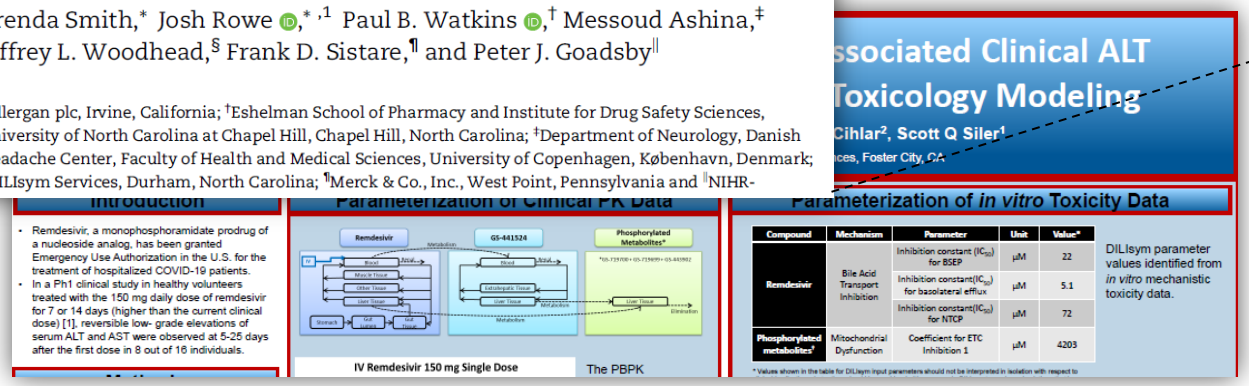
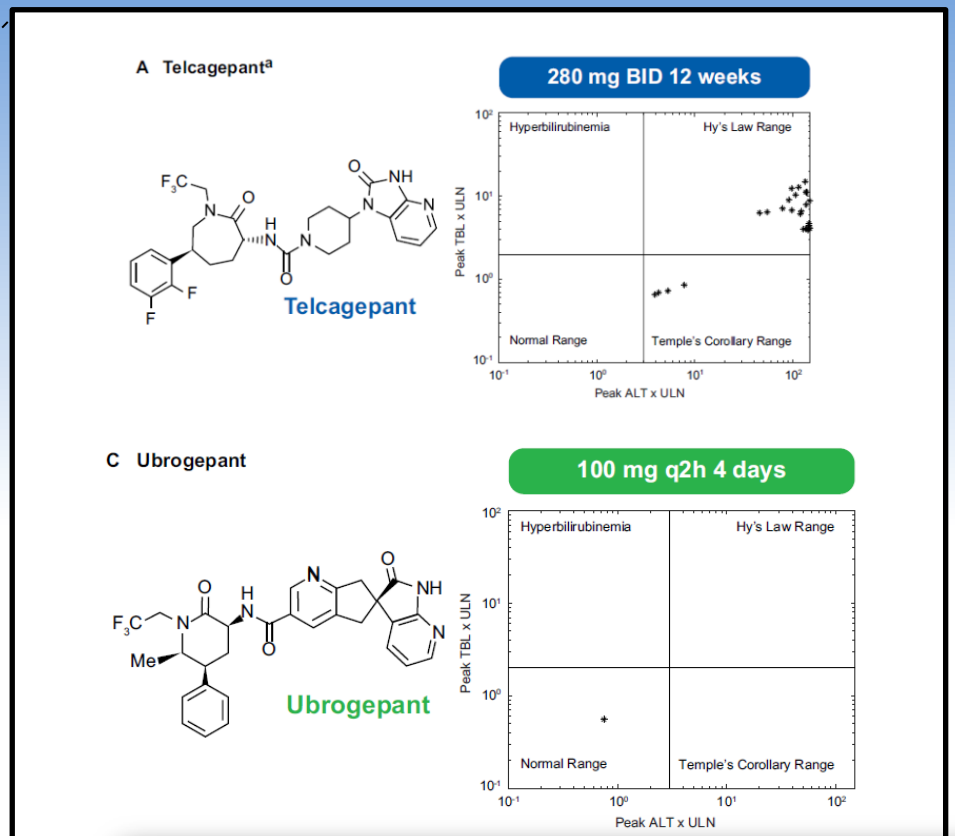
Research Article

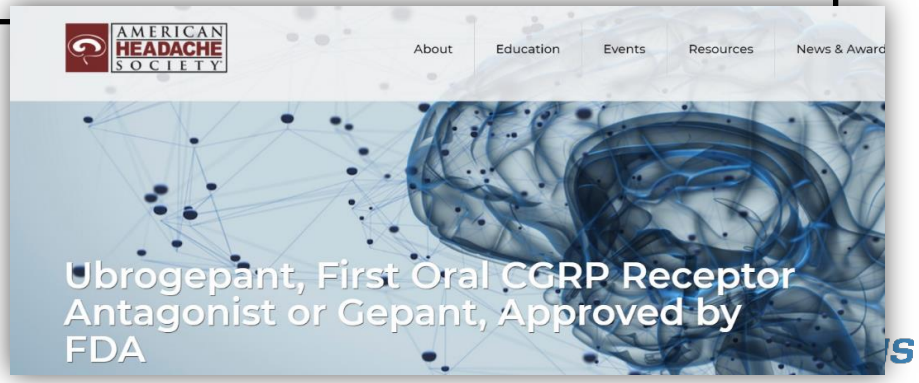
Mechanistic Investigations Support Liver Safety of Ubrogepant

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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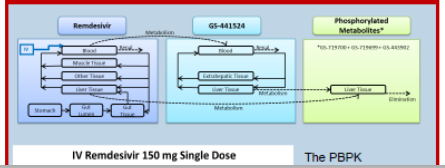

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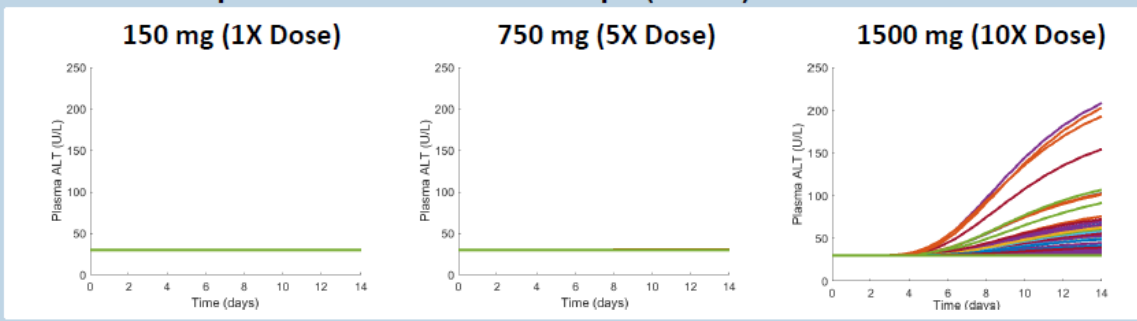

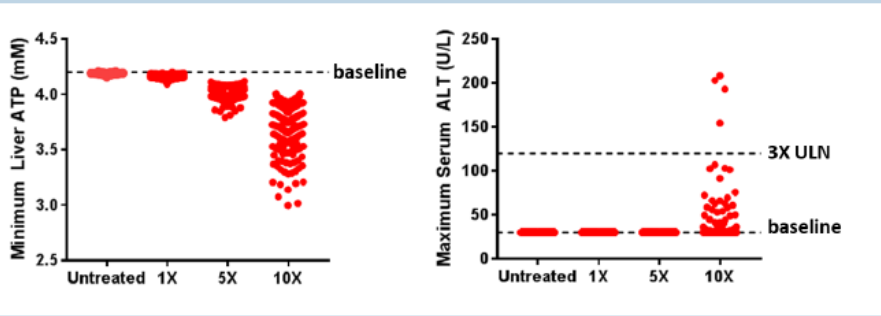

Conclusions

- 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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Q & A