DILIsym Services

A SIMULATIONS PLUS COMPANY

DILIsym® Applications in Drug Development - Perspectives from 2 Pharma Industry Executives & an Experienced Consultant

DILIsym Services Division of Simulations Plus

April 29, 2021

Meet the Cast……

Dr. Vlad Coric
CEO, Biohaven

Dr. Paul Watkins
Consultant
Professor, UNC

Dr. Brett Howell
Moderator

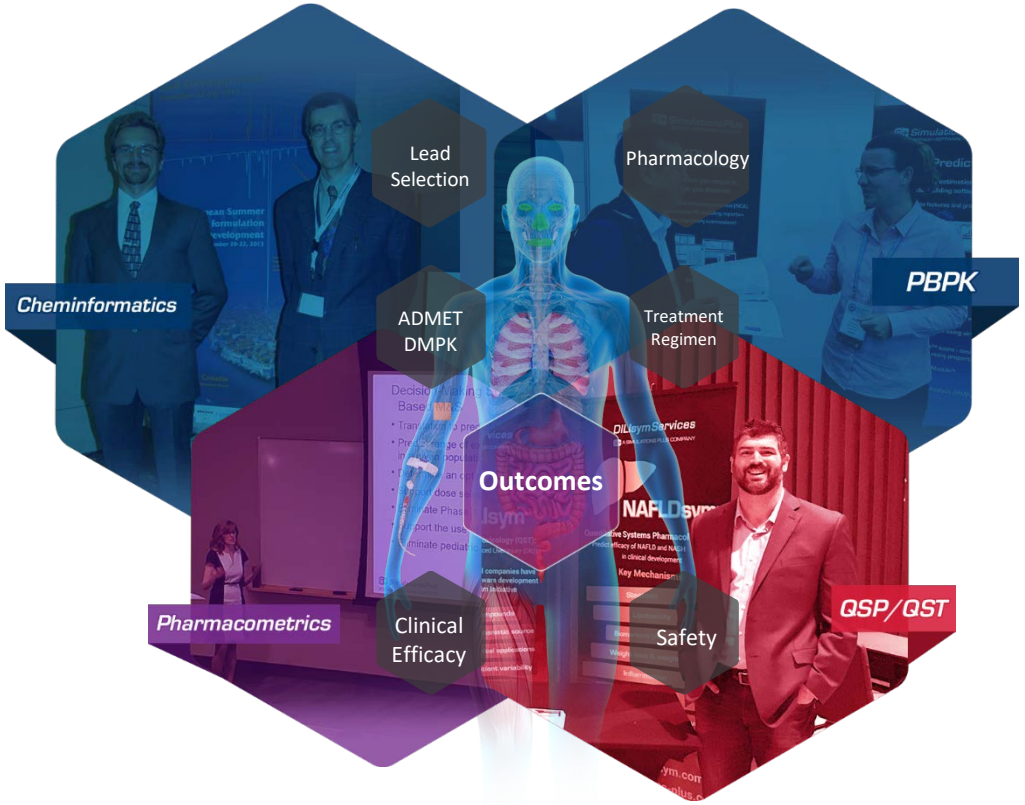
Dr. Lorenzo Pellegrini
COO, Palladio Bio

**No participants were compensated for participating in this webinar*

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!

NASDAQ: SLP

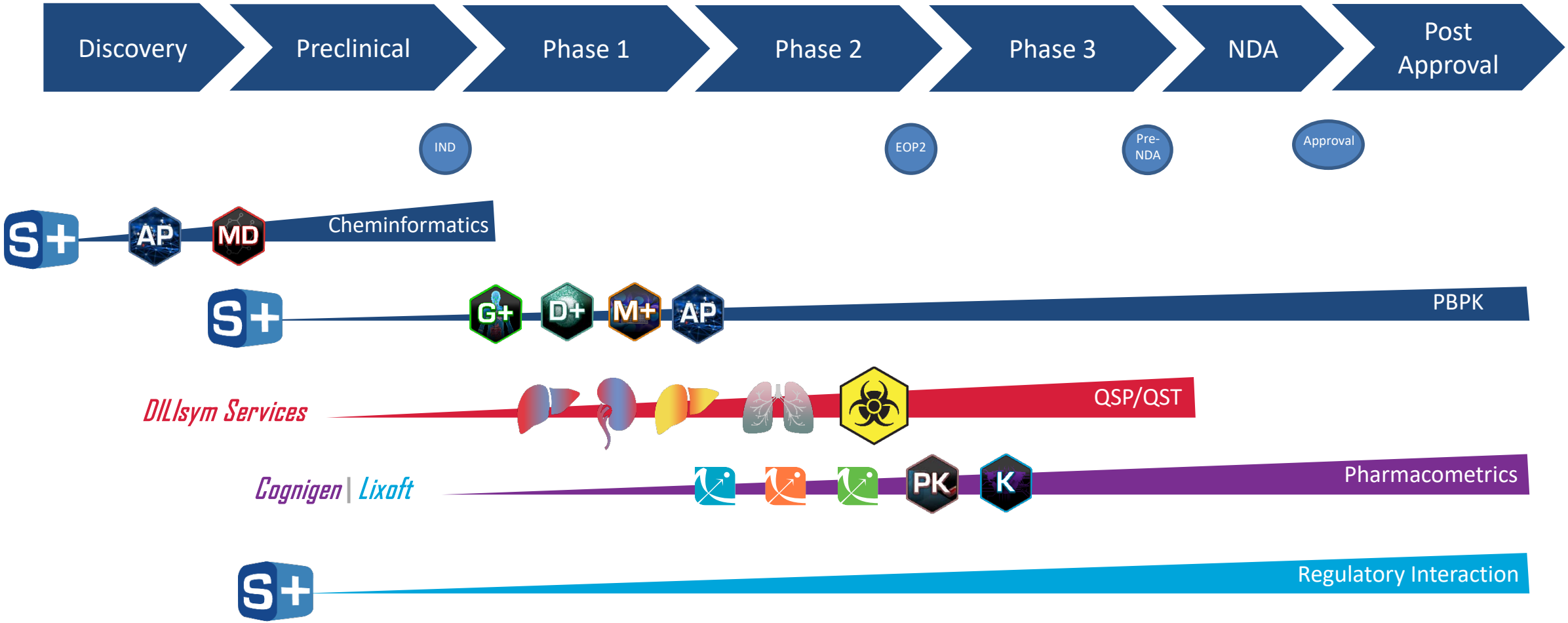
How We Can Help: Two Sides to the Company

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



NASDAQ: SLP

DILIsym Services Division of Simulations Plus: Mechanistic, QSP/QST Modeling

***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 communicate with uncompromised truth and honesty**

***Commitment*: providing quality products and exceptional services that deliver value to our partners and the people we serve**

DILIsym™ RENAsym™ IPFsym™ NAFLDsym™ RADAsym™

- **DILIsym** software licensing, training, development (DILI-sim, RENAsym consortia)
- **NAFLDsym** and **IPFsym** software licensing, training, development
- **DILIsym, NAFLDsym,** and **IPFsym** simulation consulting projects
- **Custom QSP model** development and simulation consulting projects
- Drug development consulting and data interpretation; *in vitro* assay experimental design and management
- **RENAsym** and **RADAsym** software in development

NASDAQ: SLP

DILIsym Services QST Software Aids Decisions

- Predicts drug-induced liver disease
- v8A released Q1 2019
- Includes mechanistic representation of normal hepatic biochemistry
- Evaluated >80 compounds with 40+ companies

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….***

The DILI-sim and RENAsym Consortia are Partnerships Between DILIsym Services and Pharmaceutical Companies to Minimize Organ Injury

Scientific Advisory Boards

DILIsym Services
A SIMULATIONS PLUS COMPANY

janssen

gsk GlaxoSmithKline

DILIsym

GILEAD

RENAsym

SERVIER

abbvie

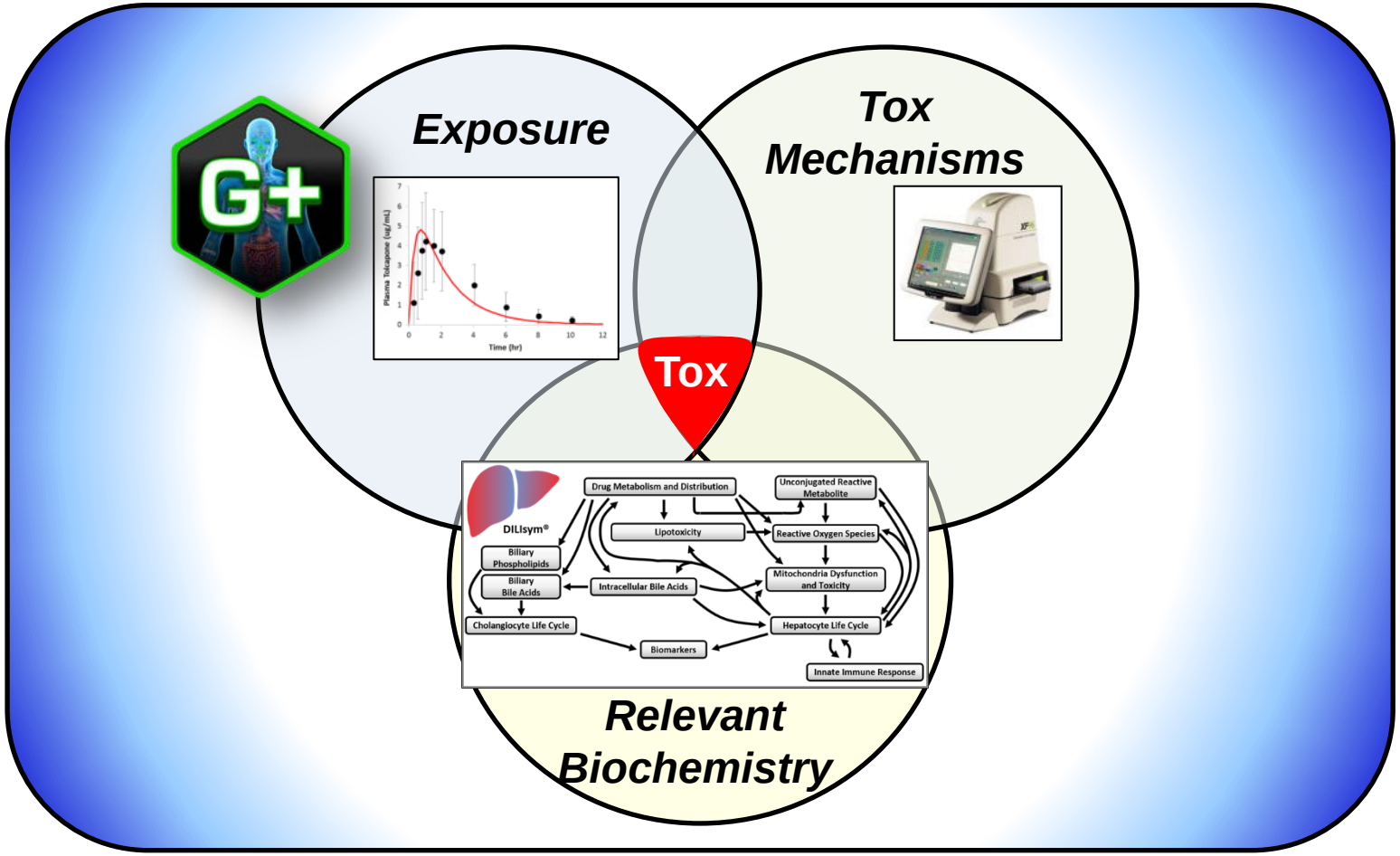
Company X – signature soon

Current DILI-sim / RENAsym Members

For a comprehensive review of progress, see *Watkins 2020, Current Opinion in Toxicology (23-24:67-73)*

- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*
- *History*
  - *Officially started in 2011*
  - *20+ major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $10 million total invested in project*
- ***At least 29 cases of use for regulatory purposes***
- ***Over 30 publications***

QST Predicts Tox via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability



Important DILIsym Application Examples

Comparing the Liver Safety Profiles of Four Next-in-Class CGRP Receptor Antagonists to the Hepatotoxic CGRP Inhibitor Telcagepant Using Quantitative Systems Toxicology Modeling

Woodhead, Jeffrey L. (1); Siler, Scott Q. (1); Howell, Brett A. (1); Watkins, Paul B (2); Conway, Charles (3)

1. DILIsym Services, Inc., a Simulations Plus company, Research Triangle Park, NC, USA

2. Institute for Drug Safety Sciences, UNC-Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA

3. Biohaven Pharmaceuticals, Inc., New Haven, CT, USA

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

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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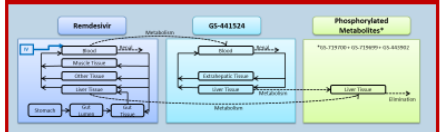
- In a Ph1 clinical study in healthy volunteers treated with the 150 mg daily dose of remdesivir for 7 or 14 days (higher than the current clinical dose) [1], reversible low- grade elevations of serum ALT and AST were observed at 5-25 days after the first dose in 8 out of 16 individuals.

Parameterization of Clinical PK Data



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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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

"In summary, DILIsym prospectively predicted improved liver safety of rimegepant, zavegepant, atogepant, and ubrogepant relative to telcagepant, and these predictions have been born out in the clinical trials conducted to date. Our results support the value of QST modeling in drug development."

	Failed CGRP (telcagepant)	CGRP-1 (Rime-gepant)	CGRP-2 (Zave-gepant)	CGRP-3 (Ato-gepant)	CGRP-4 (Ubro-gepant)
DILIsym Sims	X	✓	✓	✓	✓
Clinical Results Thus-far	X	✓	✓	✓	✓

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Pharm Res (2019) 36: 48
https://doi.org/10.1007/s11095-019-2582-y

RESEARCH PAPER

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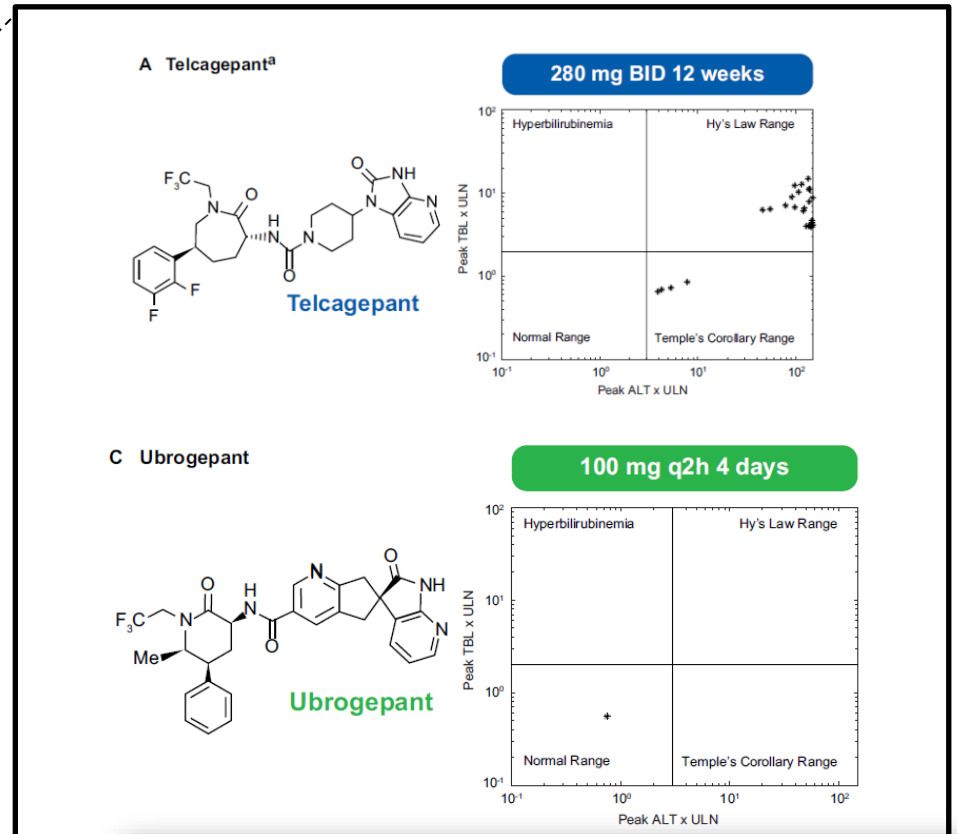
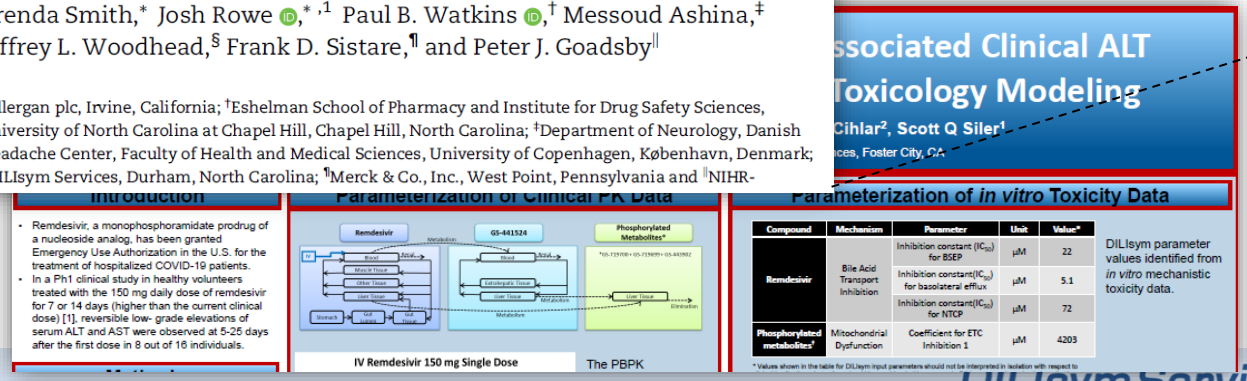
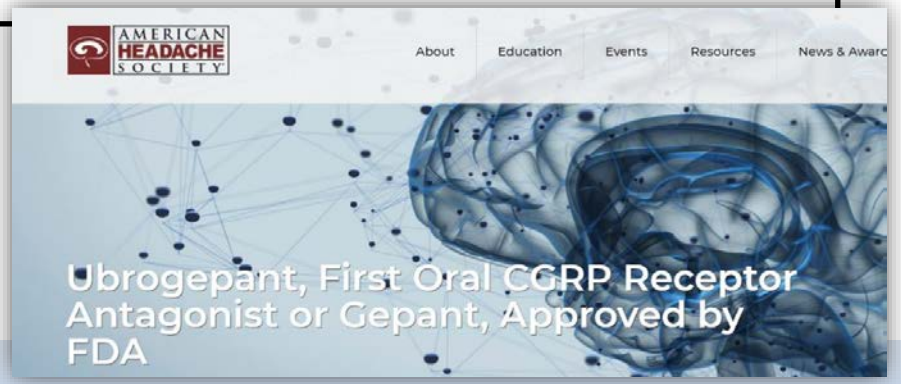
Brenda Smith,* Josh Rowe,*,[1] Paul B. Watkins,† Messoud Ashina,‡ Jeffrey L. Woodhead,§ Frank D. Sistare,¶ and Peter J. Goadsby‖

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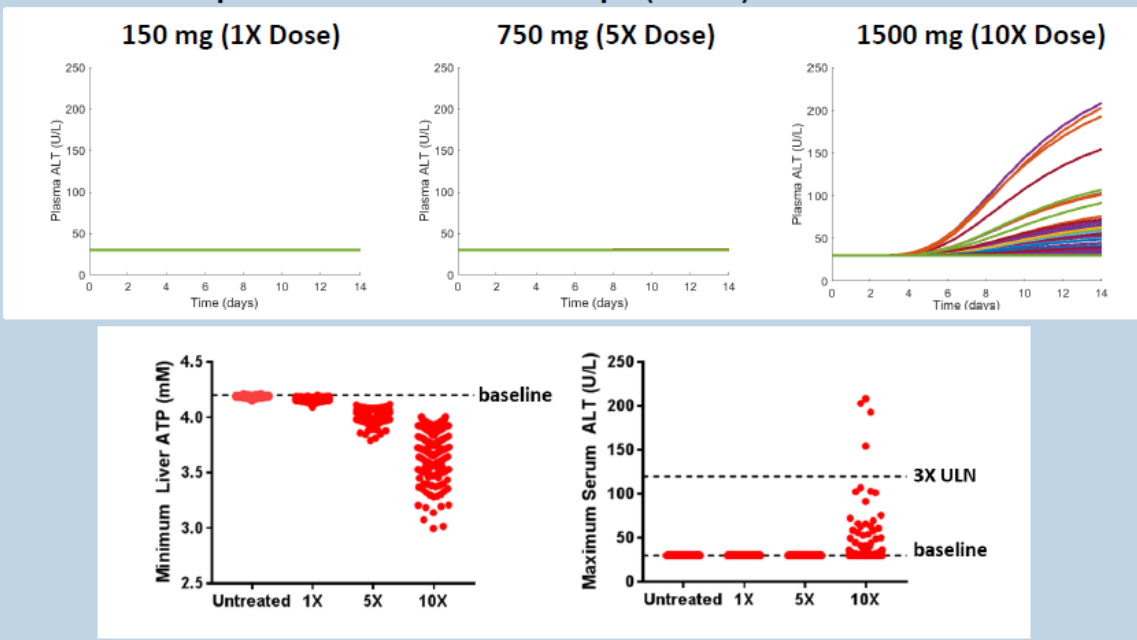
Simulated Hepatic Biomarkers in SimPops (n=300) administered remdesivir



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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Pharm Res (2020) 37:24
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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]

Application of the DILIsym® Quantitative Systems Toxicology drug-induced liver injury model to evaluate the carcinogenic hazard potential of acetaminophen

NDA	**211810**
Applicant	Daiichi Sankyo Inc
Drug	Pexidartinib (PLX3397; Turalio) from Daiichi Sankyo
Consulting Division	Division of Oncology Products 2 (DOP2)/ Office of Hematology and Oncology Products
Clinical Reviewer	Ruby Mehta, MD

Refining Liver Safety Risk Assessment: Application of Mechanistic Modeling and Serum Biomarkers to Cimaglermin Alfa (GGF2) Clinical Trials

A Mechanistic Model of Drug-Induced Liver Injury Ai the Interpretation of Elevated Liver Transaminase Le in a Phase I Clinical Trial

BA Howell[1], SQ Siler[1], LKM Shoda[1], Y Yang[1], JL Woodhead[1] and PB Watkins[1,2]

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

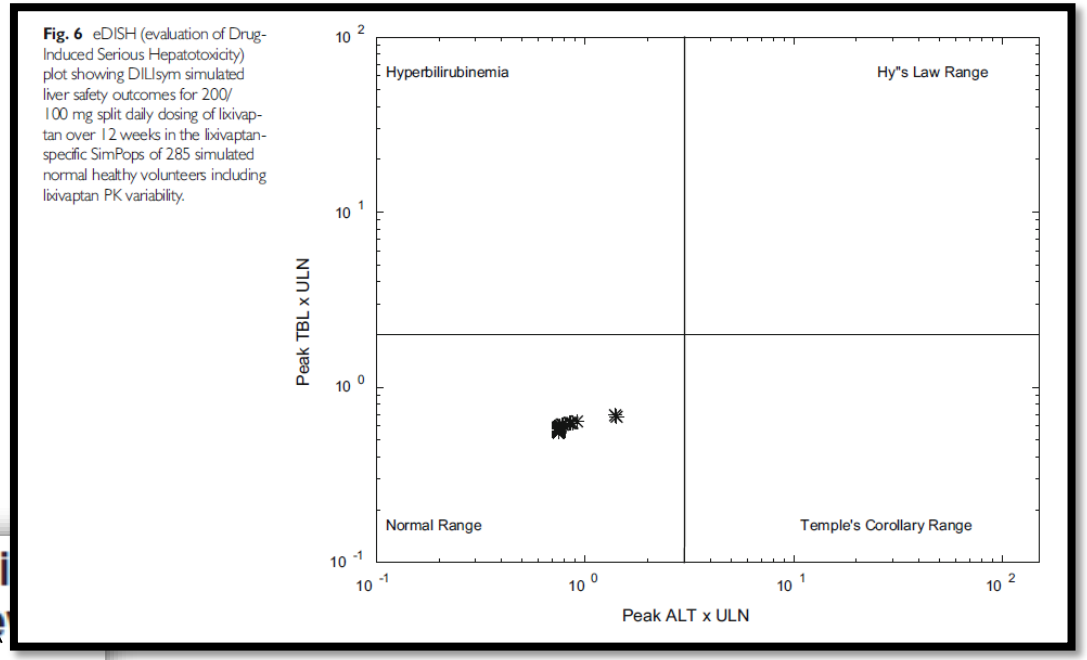

Fig. 6 eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plot showing DILIsym simulated liver safety outcomes for 200/100 mg split daily dosing of lixivaptan over 12 weeks in the lixivaptan-specific SimPops of 285 simulated normal healthy volunteers including lixivaptan PK variability.

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RESEARCH PAPER

ELSEVIER

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Application of the DILIsym® Quantitative Systems Toxicology drug-induced liver injury model to evaluate the carcinogenic hazard potential of acetaminophen

Gary Eichenbaum [a,*], Kyunghee Yang [b], Yeshitila Gebremichael [b], Brett A. Howell [b], F. Jay Murray [c], David Jacobson-Kram [d], Hartmut Jaeschke [e], Edwin Kuffner [a], Cathy K. Gelotte [f], John C.K. Lai [f], Daniele Wikoff [g], Evren Atillasoy [f]

[a] Johnson & Johnson, New Brunswick, NJ, 08901, USA
[b] DILIsym Services Inc., Research Triangle Park, NC, 27709, USA
[c] Murray & Associates, San Jose, CA, 95138, USA

Clinical Reviewer | Ruby Mehta, MD

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CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

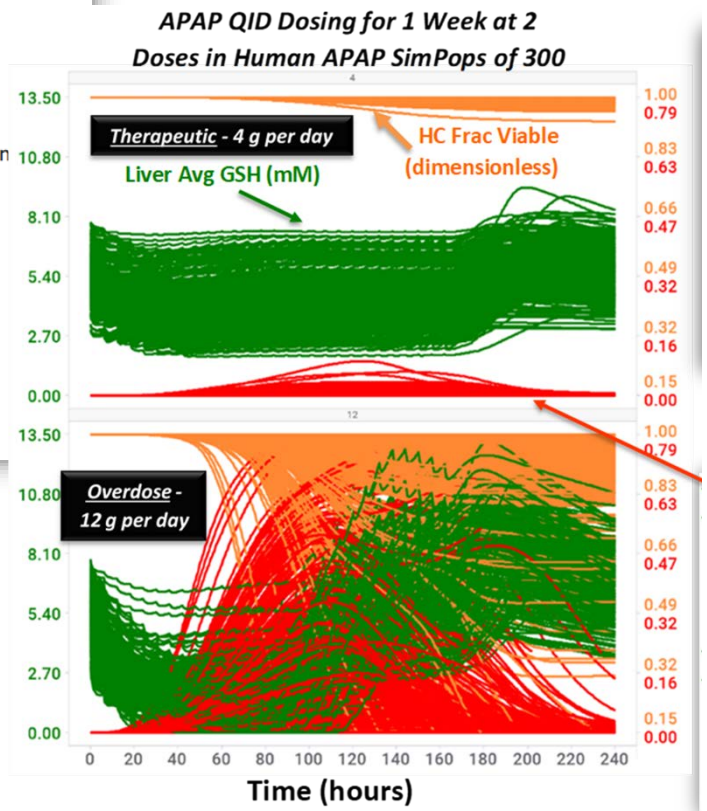
An Integrated Weight of Evidence Assessment of the Carcinogenicity Hazard Potential of Acetaminophen

Information for the California Carcinogen Identification Comm

Submitted by the:

Consumer Healthcare Products Association

November 4, 2019



Simulations including population variability support that across a wide array of patient backgrounds, acetaminophen exposure only results in significant oxidative stress or DNA effects under conditions that cause cell death

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Clinical Reviewer	Ruby Mehta, MD Medical Officer, Division of Gastroenterology & Inborn Errors Products (DGIEP)
Team Leader, DGIEP	Stephanie O. Omokaro, MD
Associate Director, Office of Pharmacovigilance & Epidemiology (OPE)	Mark Avigan, MD, CM
Date of Memo	July 28, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211810Orig1s000

A.3. Mechanistic Studies

Possible mechanisms for liver toxicity of pexidartinib and its *N*-glucuronide metabolite, ZAAD-1006a, were assessed by DILIsym® analysis based on *in vitro* hepatotoxicity data, the phase 3 study data (PLX108-10), simulations of chemical hepatic exposure, and simulations of hepatotoxicity mechanisms.

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jury Aids

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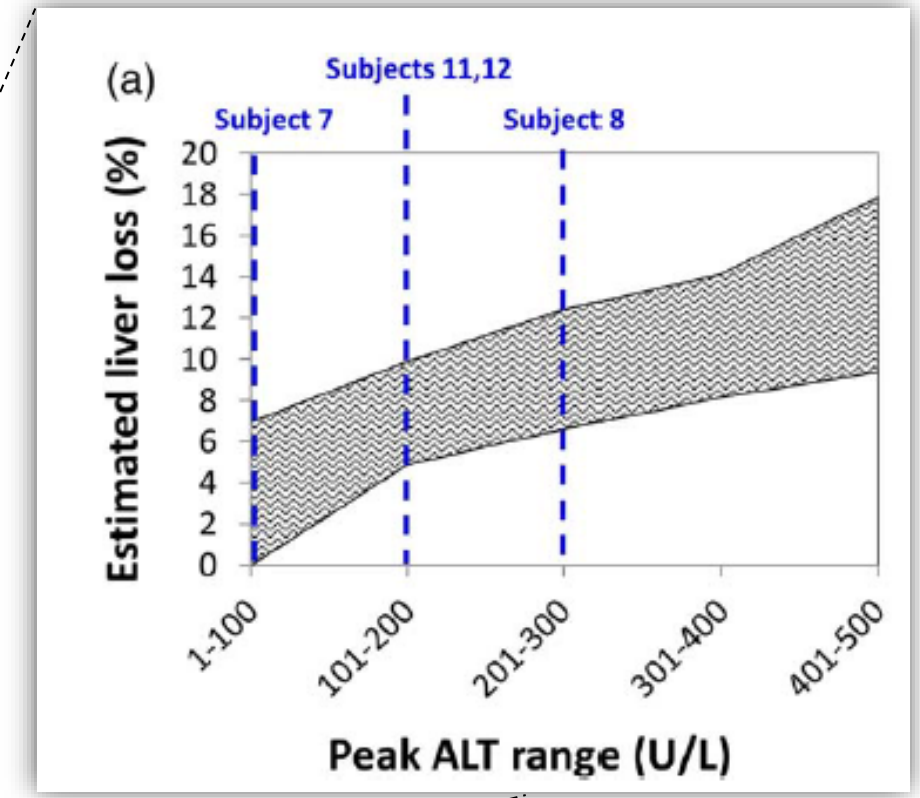

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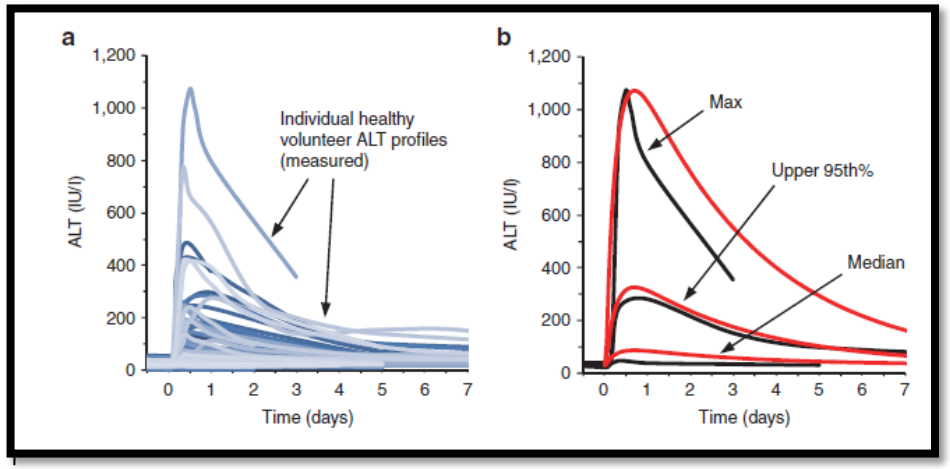
Application of the DILIsym® Quantitative Systems Toxicology drug-induced liver injury model to evaluate the carcinogenic hazard potential of acetaminophen

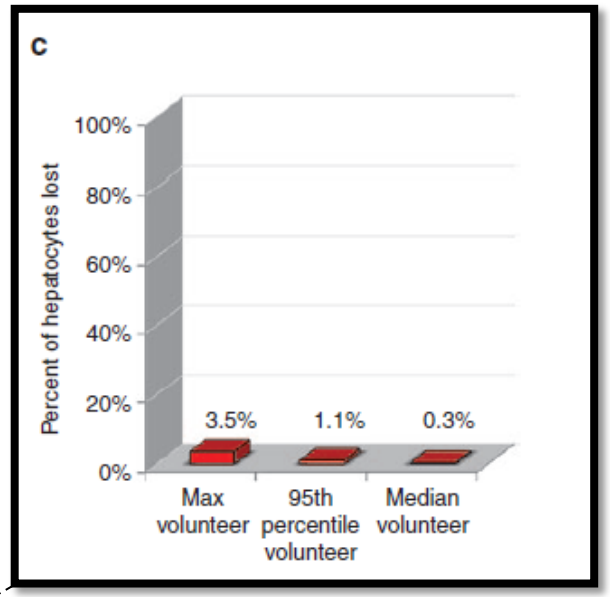
NDA	**211810**
Applicant	Daiichi Sankyo Inc
Drug	Pexidartinib (PLX3397; Turalio) from Daiichi Sankyo
Consulting Division	Division of Oncology Products 2 (DOP2)/ Office of Hematology and Oncology Products
Clinical Reviewer	Ruby Mehta, MD

Refining Liver Safety Risk Assessment: Application of Mechanistic Modeling and Serum Biomarkers to Cimaglermin Alfa (GGF2) Clinical Trials

A Mechanistic Model of Drug-Induced Liver Injury Aids the Interpretation of Elevated Liver Transaminase Levels in a Phase I Clinical Trial

BA Howell[1], SQ Siler[1], LKM Shoda[1], Y Yang[1], JL Woodhead[1] and PB Watkins[1,2]





Take Home Message…….

- DILIsym has helped many drug developers and investors with key decisions and submissions
- DILIsym can help your program or project as well – consulting or licensing!
- Let’s chat with our panel and get their perspectives……

Meet the Cast……

Dr. Vlad Coric
CEO, Biohaven

Dr. Paul Watkins
Consultant
Professor, UNC

Dr. Brett Howell
Moderator

Dr. Lorenzo Pellegrini
COO, Palladio Bio

**No participants were compensated for participating in this webinar*