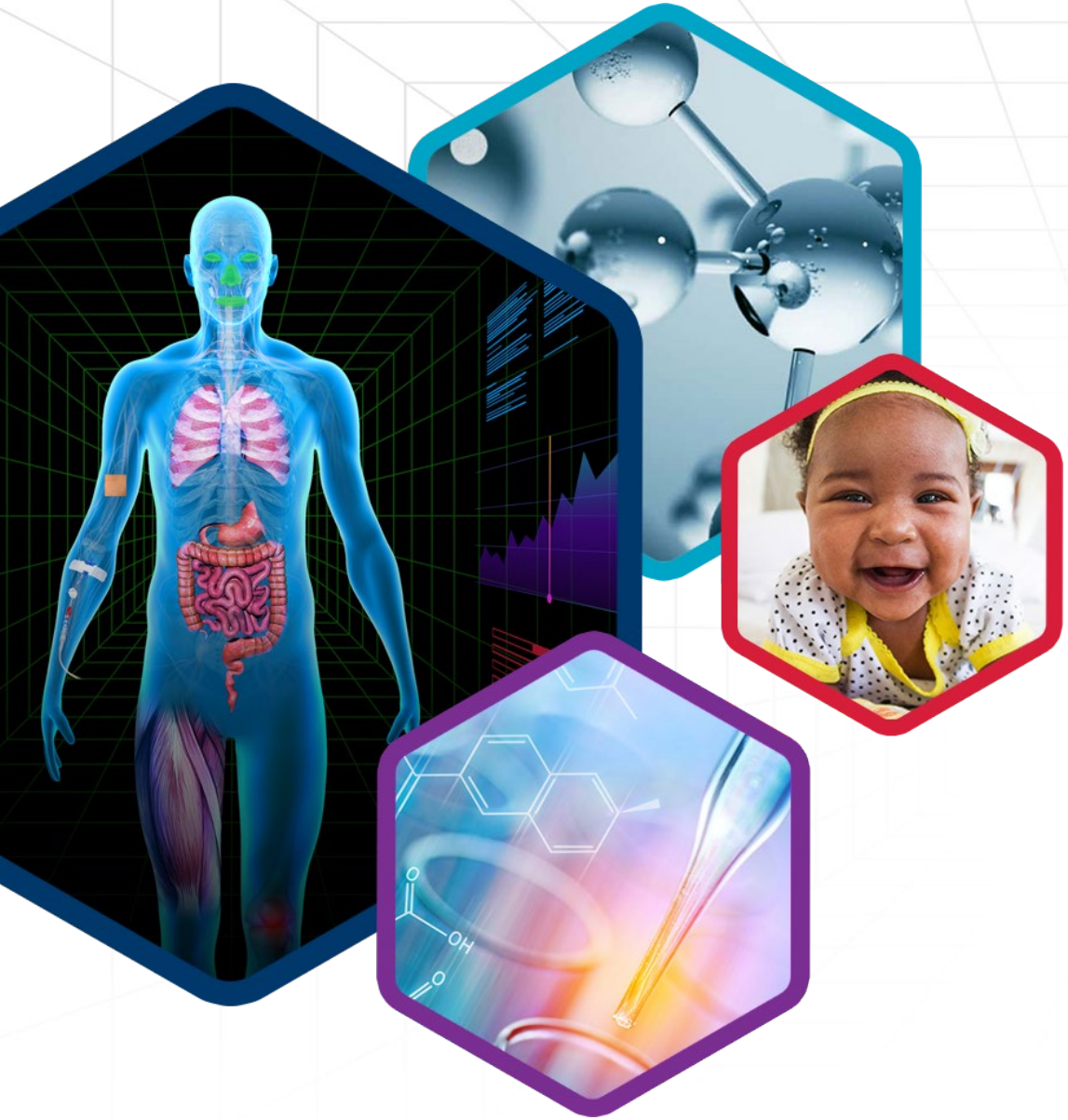


SimulationsPlus

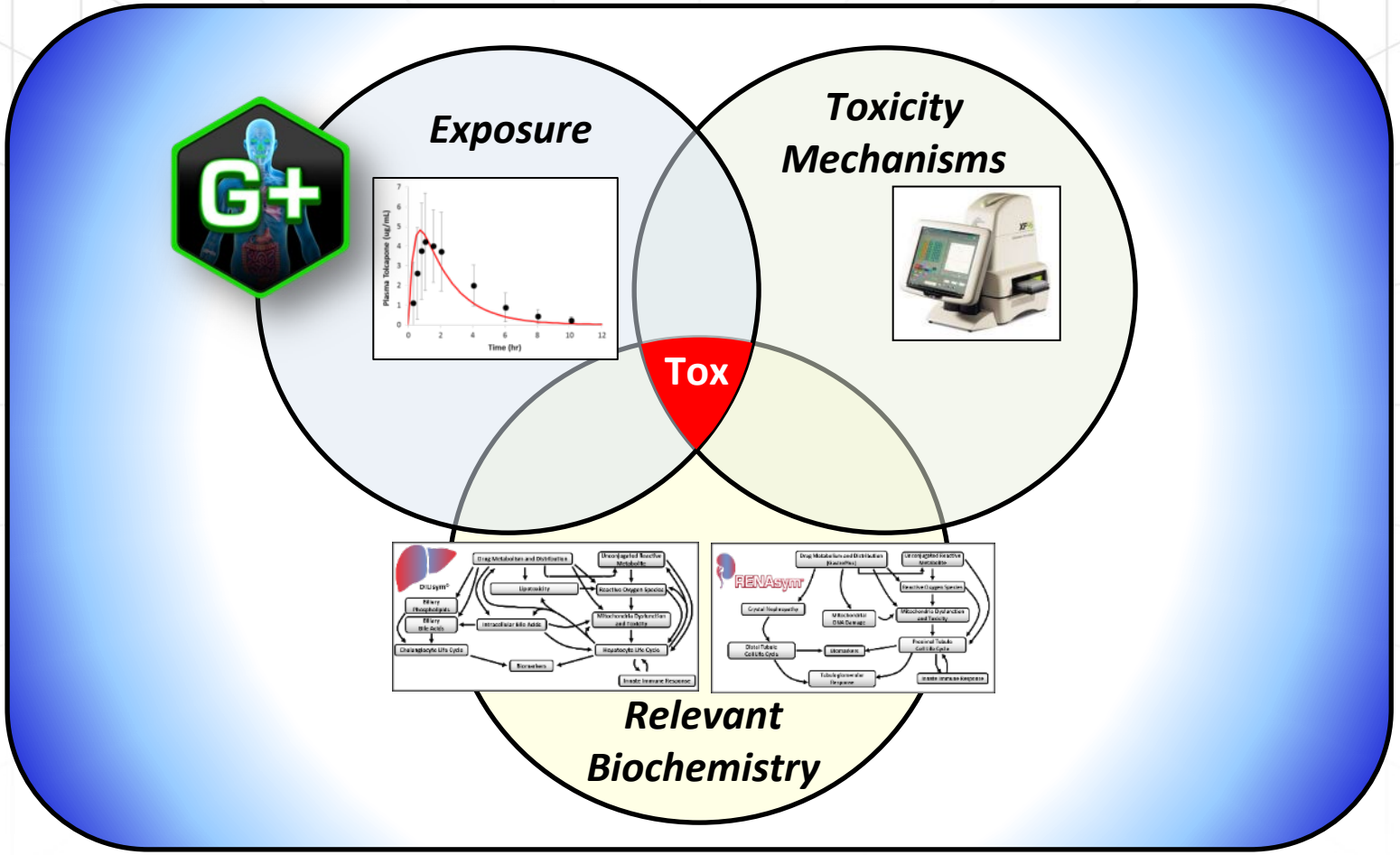
Cognigen | DILIsym Services | Lixoft

Advancing Calcitonin Gene-Related Peptide Receptor Antagonists Using Quantitative Systems Toxicology Modeling to Characterize Next-in-Class Compounds Compared to the Hepatotoxic First in Class Telcagepant

Jeff Woodhead, Ph.D.

February 16, 2022

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



DILIsym Utilizes Various Data Types to Inform Decisions

DMPK and 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

Data Collected for Quantitative DILI Mechanism Info

- **Oxidative stress** *(high content imaging)*
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity** *(XF Analyzer)*
  - *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:

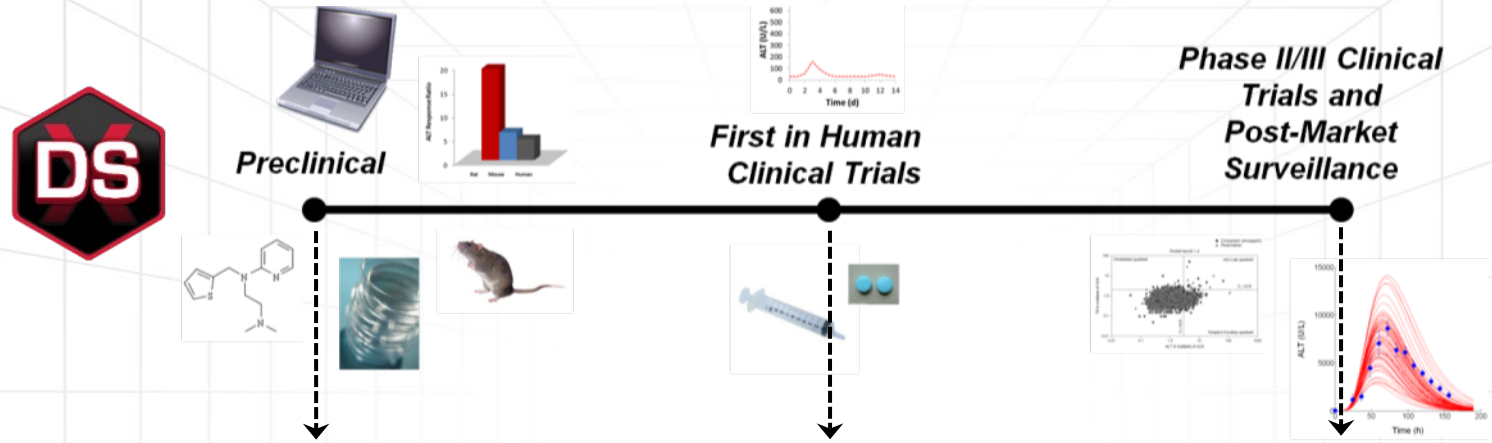
- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

Clinical Data / Information

- **Dosing Protocols, fasting/fed state, meal times**
- **Patient types (NHV, disease, etc.)**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

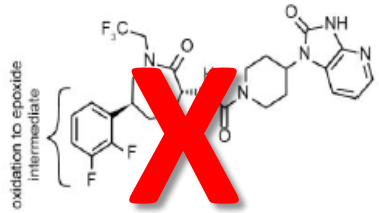
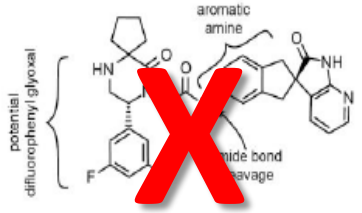
Applications of DILIsym Along the Drug Development Pipeline

Predictions of hepatotoxicity for humans and preclinical animal models



• Mechanism exploration • **Rank candidates for DILI potential** • Extrapolation from animal and *in vitro* findings to humans	• **Dose optimization (risk versus presumed benefit)** • Infer magnitude of injury based on measured biomarkers • Extrapolation from healthy volunteers to patient groups • Guide incorporation of emerging biomarker measurements in clinical trials • Analysis of mechanisms underlying observed liver signals	• Inform choice and timing of biomarker measurement • Aid identification of risk factors leading to personalized medicine approaches • Analysis of mechanisms underlying observed liver signals

Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]	MK-3207[b]
Structure[d]		
Potency IC_{50}[e]	2.2 nM	0.12 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin

Next-in-class Compounds

- Ubrogepant ?
- Rimegepant ?
- Atogepant ?
- Zavegepant ?

CGRP Receptor Antagonist Project Objectives

- Project undertaken when no large Phase 3 clinical trials had been reported for next-in-class compounds
  - Next-in-class representations are **purely predictive** at this point
- Replicate the clinically observed toxicity for telcagepant
- Determine potential safety/toxicity of novel compounds rimegepant and zavegepant compared to telcagepant
  - Rimegepant has clinical exposure data; zavegepant has not been tested in humans
- Determine potential safety/toxicity of competitor compounds ubrogepant and atogepant
  - No clinical data available for either; representation based entirely on IVIVE

Data Used for CGRP Antagonist Compound Projects

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*

- **Telcagepant**: published clinical PK data
- **Rimegepant**: internal clinical PK data available
- **Zavegepant**: ADMET Predictor informed by animal data and intra-nasal dosing route
- **Atogepant**: pure IVIVE using ADMET Predictor
- **Ubrogepant**: pure IVIVE using ADMET Predictor

Data Collected for Quantitative DILI Mechanism Info

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

- Full in vitro data set collected for all five compounds

CGRP Antagonist Compound Simulation Results

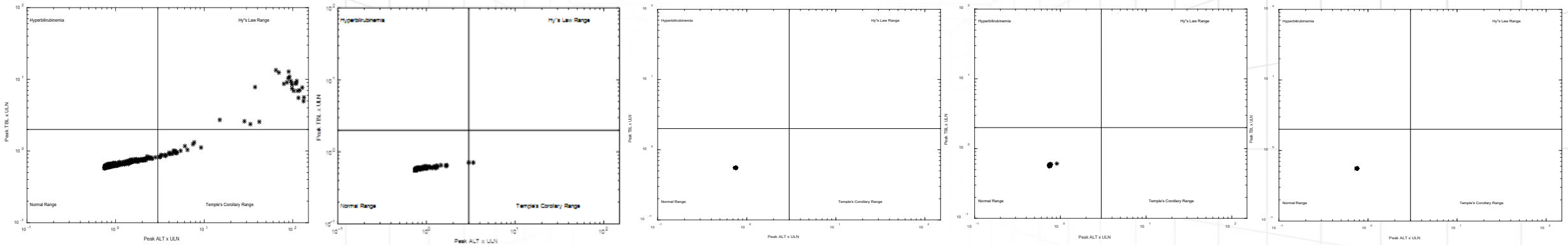
Telcagepant; 140 mg BID, 12 weeks, high ETCi

Rimegepant; 75 mg QD, alternate day dosing, 14 total doses over 28 days

Zavegepant; 20 mg IN or 750 mg PO or 7.5 mg IV, 25 straight days

Atogepant; 60 mg BID, 12 weeks

Ubrogepant; 100 mg QD, 25 straight days



- Telcagepant toxicity correctly predicted by DILIsym
- Rimegepant predicted to be safe at clinical doses, with mild ALT elevations occurring only in extreme dosing conditions
- Zavegepant, atogepant, and ubrogepant all predicted to be safe with substantial safety margins

CGRP Antagonist Compound Simulation Results

- Mechanistic results predict difference between telcagepant and other CGRP antagonist compounds
  - Telcagepant toxicity predicted to be due to mixed-mode bile acid transporter inhibition and mitochondrial ETC inhibition
  - Other compounds' signals generally due to other mechanisms

Compound	Oral Dosing Protocol	Simulated* ALT > 3X ULN	Observed ALT > 3X ULN in Clinic
Telcagepant – Original ETC	140 mg BID, 12 weeks	17.5% (50/285)	1.9% (5/263)
	280 mg BID, 12 weeks	76.1% (217/285)	3.2% (8/265)
Telcagepant – Alternate ETC	140 mg BID, 12 weeks	0.0% (0/285)	1.9% (5/263)
	280 mg BID, 12 weeks	7.72% (22/285)	3.2% (8/265)
Rimegepant	75 mg QD, alternate day dosing, 14 total doses	0.35% (1/285)	--
	75 mg QD, 5 days on, 1 day off, 25 total doses	0.7% (2/285)	--
	75 mg QD, daily dosing for 25 days, 25 total doses	1% (3/285)	--
Zavegepant	750 mg oral QD, 25 days, 25 total doses	0.0% (0/285)	
	7.5 mg IV QD, 25 days, 25 total doses	0.0% (0/285)	
Atogepant	60 mg BID, 12 weeks	0% (0/285)	
	300 mg BID, 12 weeks	0.3% (1/285)	
	600 mg BID, 12 weeks	10.2% (29/285)	
Ubrogepant	100 mg QD, 25 days	0% (0/285)	
	500 mg QD, 25 days	1.4% (4/285)	
	1000 mg QD, 25 days	11.6% (33/285)	

Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

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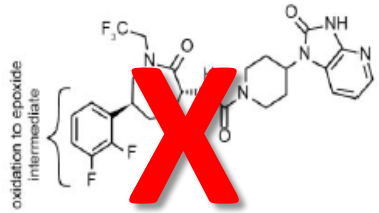
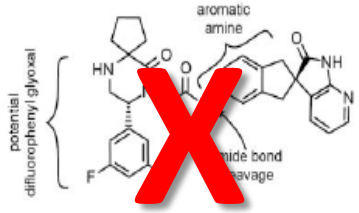
Structure[d]		
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Next-in-class Compounds

- Ubrogepant ✓
- Rimegepant ✓
- Atogepant ✓
- Zavegepant ✓

FDA Approval Achieved for Rimegepant, Ubrogepant, and Atogepant

Allergan Receives U.S. FDA Approval for UBRELVY™ for the Acute Treatment of Migraine with or without Aura in Adults

FDA APPROVES BIOHAVEN'S NURTEC® ODT (RIMEGEPANT) FOR PREVENTION: NOW THE FIRST AND ONLY MIGRAINE MEDICATION FOR BOTH ACUTE AND PREVENTIVE TREATMENT

FDA Approves QULIPTA™ (atogepant), the First and Only Oral CGRP Receptor Antagonist Specifically Developed for the Preventive Treatment of Migraine

- Rimegepant, ubrogepant, and atogepant all have received FDA approval
  - No black-box warning for hepatotoxicity
- Zavegepant clinical trials continue
  - No hepatotoxicity observed thus far

Biohaven Reports Positive Topline Results from Pivotal Migraine Trial of Intranasal Zavegepant Demonstrating Ultra-Rapid Pain Relief by 15 minutes; Prepares for Submission of New Drug Application

Ubrogepant and Telcagepant Were Part of a Separate Simulation Project

Mechanistic Investigations Support Liver Safety of Ubrogepant

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Jeffrey L. Woodhead,§ Frank D. Sistare,¶ an[illegible]

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University of North Carolina at Chapel Hill, Chapel Hill, North[illegible]
Headache Center, Faculty of Health and Medical Sciences, Un[illegible]
§DILIsym Services, Durham, North Carolina; ¶Merck & Co., Inc[illegible]
Wellcome Trust King's Clinical Research Facility, SLaM Biome[illegible]
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Brenda Smith and Josh Rowe contributed equally as first author.

Table 2. DILIsym Predictions for Telcagepant, MK-3207, and Ubrogepant in a Simulated Patient Population of Healthy Volunteers

Compound	Dosing Protocol	Simulated ALT > 3× ULN[a]	Clinical ALT > 3× ULN
Telcagepant[b]	280 mg BID 12 weeks	12.6% (36/285)	3.2% (8/253) (Ho *et al.*, 2014)
	140 mg BID 12 weeks	0% (0/285)	1.9% (5/258) (Ho *et al.*, 2014)
MK-3207[c]	200 mg q2h, 2 daily doses (400 mg daily dose), for 14 days	3.5% (10/285)	42% (5/12) among individuals dosed for more than 1 week; most responding were given 600–900 mg per day
	300 mg q2h, 2 daily doses (600 mg daily dose), for 14 days	7% (20/285)	
	450 mg q2h, 2 daily doses (900 mg daily dose), for 14 days	10.2% (29/285)	
Ubrogepant	100 mg q2h, 4 days	0% (0/285)	N/A
	1000 mg q2h, 4 days	0% (0/285)	N/A
	100 mg QD, 8 days	0% (0/285)	N/A
	1000 mg QD, 8 days	0% (0/285)	N/A
	50 mg QD, 2 days on, 2 days off for 56 days, 28 total doses	0% (0/285)	N/A
	100 mg QD, 2 days on, 2 days off for 56 days, 28 total doses	0% (0/285)	0.8% 2/256 (Goadsby *et al.*, 2019)
	1000 mg QD, 2 days on, 2 days off for 56 days, 28 total doses	0% (0/285)	N/A
	50 mg q2h, 28 straight days, 56 total doses	0% (0/285)	N/A

[a]ULN in DILIsym is 40 U/l.
[b]The mechanisms involved in the predicted liver injury for telcagepant were mainly inhibition of bile salt transport, with a lesser contribution of mitochondrial electron transport inhibition and no contribution of oxidative stress.
[c]The mechanisms involved in the predicted liver injury for MK-3207 were competitive bile salt export pump inhibition and inhibition of mitochondrial electron transport, with oxidative stress being a minor contributor.
Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal.

Comparison Between Ubrogepant and Telcagepant Results Demonstrate Robustness of DILIsym Approach

This Project

Compound	Dosing Protocol	Simulated* ALT > 3X ULN**	Clinical ALT > 3X ULN***
MK-3207, Competitive BSEP Inhibition, no RM	200 mg, 2 daily doses 2 hours apart (400 mg daily dose), for 14 days	3.5% (10/285)	42% (5/12) amongst individuals dosed for more than 1 week; most responding were given 600 – 900 mg per day
	300 mg, 2 daily doses 2 hours apart (600 mg daily dose), for 14 days	7% (20/285)	
	450 mg, 2 daily doses 2 hours apart (900 mg daily dose), for 14 days	10.2% (29/285)	
Telcagepant	280 mg BID 12 weeks	12.6% (36/285)	3.2% (8/265)
	140 mg BID 12 weeks	0% 0/285	1.9% (5/263)
Ubrogepant	100 mg q.d. for 8 days	0% (0/285)	Not known at time of simulation
	100 mg q2h (200 mg per day), 2 daily doses, for 4 days	0% (0/285)	
	100 mg q.d. for 2 days, 2 days off, 56 days total of dosing with 28 total doses	0% (0/285)	

Published in Smith et al. 2021

Compound	Oral Dosing Protocol	Simulated* ALT > 3X ULN	Observed ALT > 3X ULN in Clinic
Telcagepant – Original ETC	140 mg BID, 12 weeks	17.5% (50/285)	1.9% (5/263)
	280 mg BID, 12 weeks	76.1% (217/285)	3.2% (8/265)
Telcagepant – Alternate ETC	140 mg BID, 12 weeks	0.0% (0/285)	1.9% (5/263)
	280 mg BID, 12 weeks	7.72% (22/285)	3.2% (8/265)
Ubrogepant	100 mg QD, 25 days	0% (0/285)	
	500 mg QD, 25 days	1.4% (4/285)	
	1000 mg QD, 25 days	11.6% (33/285)	

Executive Summary

- DILIsym correctly represented observed hepatotoxicity of telcagepant
- DILIsym correctly **predicted** safety of four next-in-class compounds
  - All pure predictions at the time simulations were completed
- DILIsym predicted qualitatively similar results using two separate *in vitro* data sets and PBPK model sources
  - Demonstrates robustness of DILIsym approach