Hitting the Sweet Spot: Mechanism-Based Modeling to Evaluate the Interplay of Liver Compound Exposure and Liver Toxicity to Identify Safe Dosing Regimens

Lisl K.M. Shoda, PhD

Phoenix, AZ

November 10 - 13, 2024

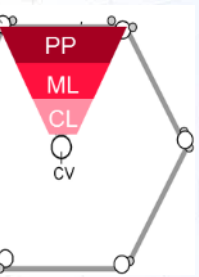
Disclaimer: Simulations Plus QSP Services are developed and provided as an educational tool based on assessment of the current scientific and clinical information, and accepted approaches for drug safety and efficacy. The resultant data, suggestions, and conclusions ("Guidelines") should not be considered inclusive of all proper approaches or methods, and they cannot guarantee any specific outcome, nor establish a standard of care. These Guidelines are not intended to dictate the treatment of any particular patient. Patient care and treatment decisions should always be based on the independent medical judgment of health care providers, given each patient's individual clinical circumstances.

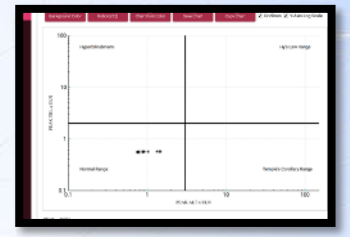
Reviving a Compound with Demonstrated Liver Safety Concerns

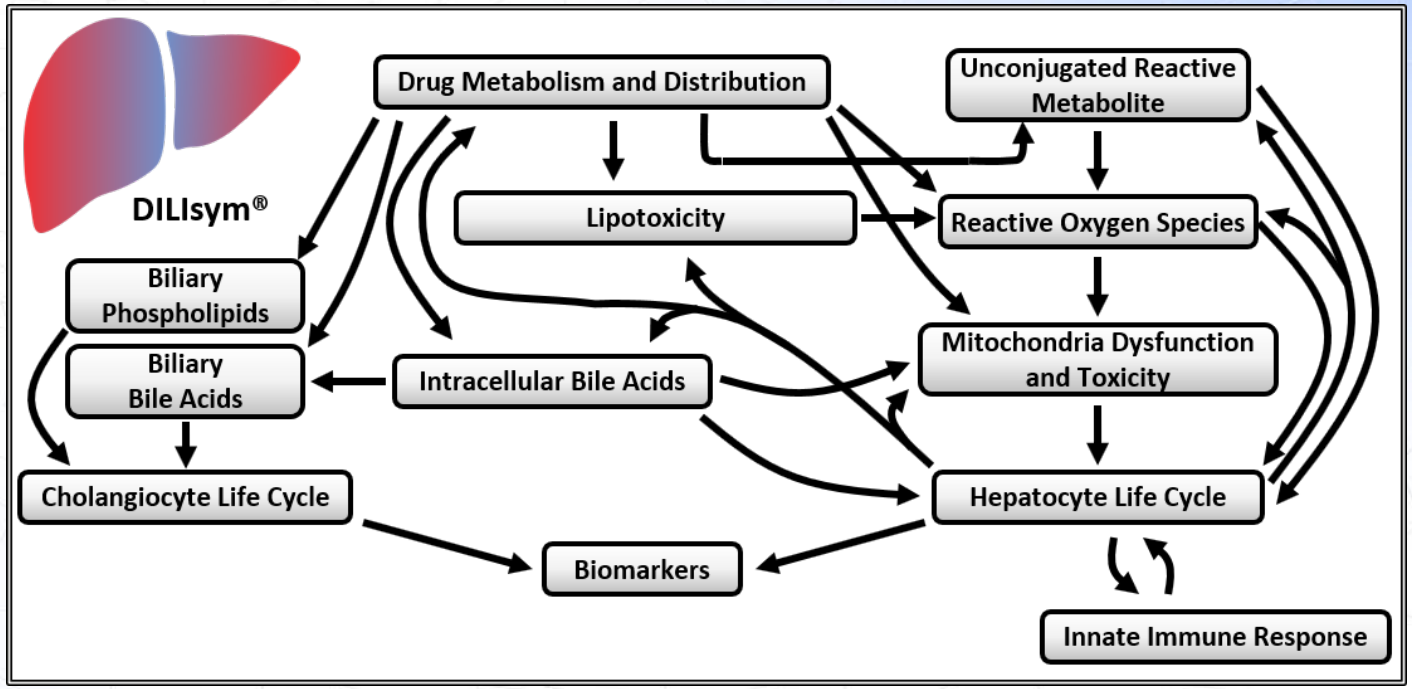
- Emvododstat: a dihydroorotate dehydrogenase (DHODH) inhibitor
  - DHODH is a key enzyme in pyrimidine synthesis
- Clinical development for treatment of solid tumors halted after two patients experienced drug-induced liver failure
- Preclinical data suggested potential efficacy in leukemic malignancies (e.g., acute myeloid leukemia) at lower doses
- ***Is it reasonable to anticipate liver safety with lower doses?***
- Project: utilize DILIsym, a Quantitative Systems Toxicology (QST) model, to retrospectively validate liver safety issues using prior clinical protocols and prospectively predict liver safety with planned clinical protocols

Evaluating Drug-Induced Liver Injury (DILI) in DILIsym

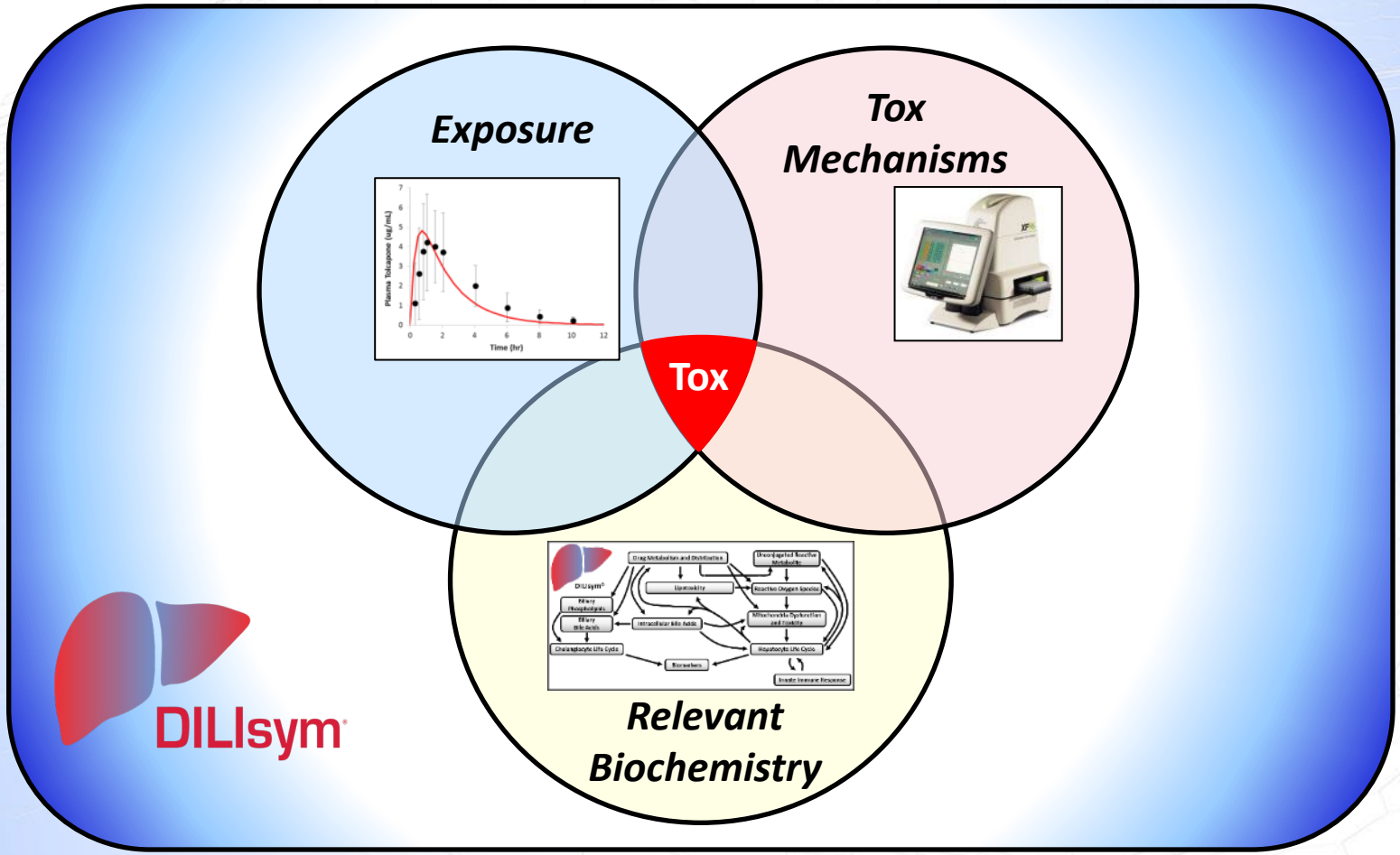
- Multiple species: human, rat, mouse, and dog
  - Population variability
- Three primary acinar zones of the liver represented
- Essential cellular processes represented to multiple scales in interacting sub-models
- Over 90 detailed representations of validation compounds with >80% success and **zero false positive predictions**
- Single and combination drug therapies







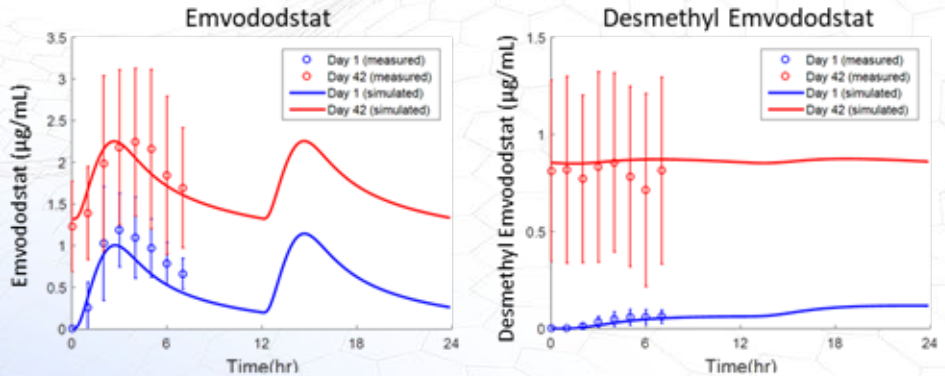
QST Predicts DILI by Integrating Compound Liver Exposure, Mechanisms of Toxicity, and Inter-Individual Variability



PBPK Models of Emvododstat and O-Desmethyl Emvododstat Optimized and Validated Against Clinical Data

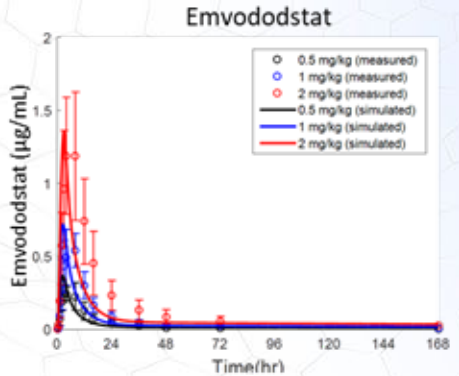
Optimization

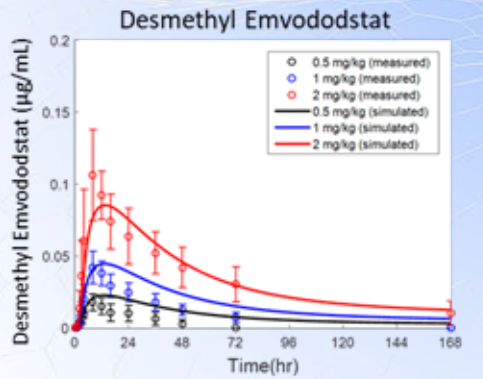
A Study 003 Stage 2 (100 mg BID)



Optimization

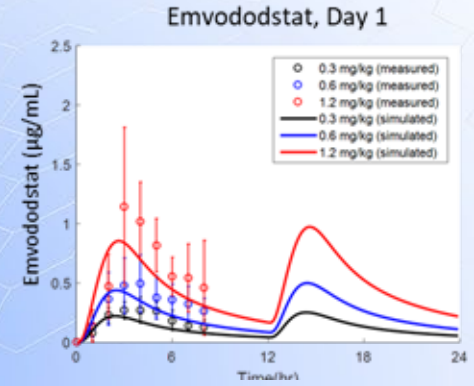
B Study 006 (0.5 – 2 mg/kg single dose)

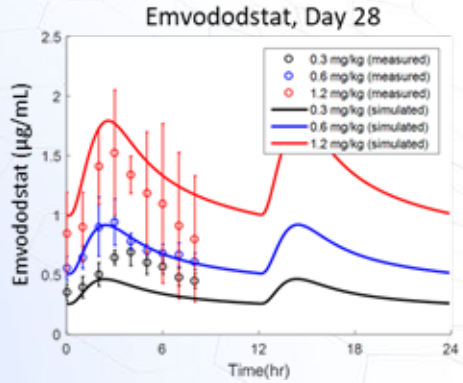


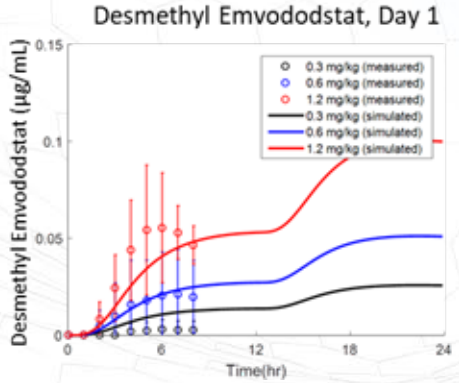


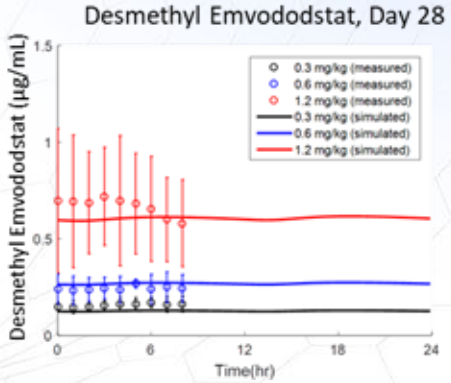
Validation

C Study 003 (0.3 – 1.2 mg/kg BID)



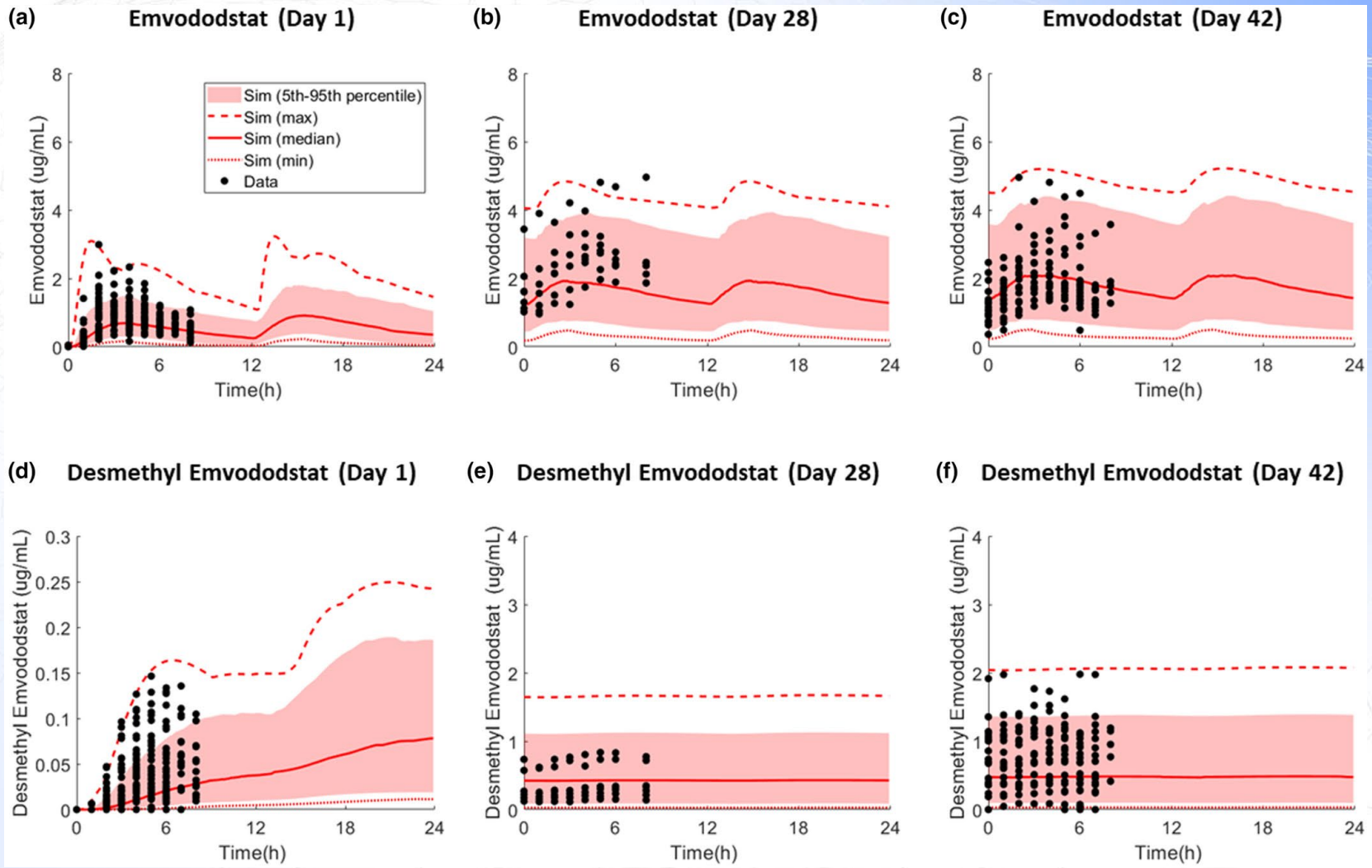






Measured Emvododstat and O-Desmethyl Emvododstat PK Variability Reproduced in SimPops

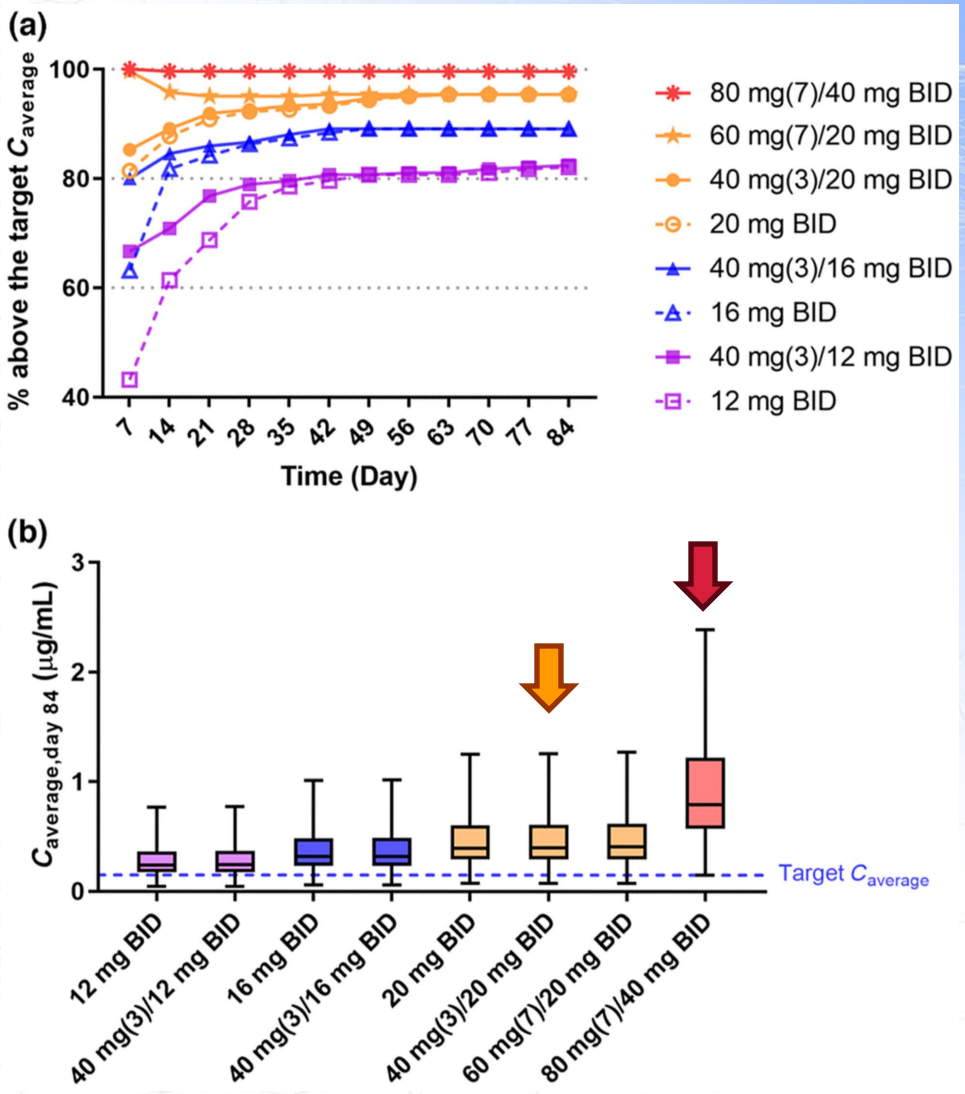
- Variability imposed on 15 PK parameters
- Metabolism V_{max} distributions informed by published literature
- Variability optimized to reflect clinical data
- SimPops span observed concentration ranges, sometimes extending beyond the min/max values by design
- Predicted liver concentrations drove interaction with toxicity mechanisms



Application of PBPK Model and PK SimPops to Identify Dosing Protocols that Achieved Target $C_{average}$

- Eight different dosing regimens simulated in N=285 PK SimPops
  - Four different maintenance doses ± loading doses of seven or three days
- Loading doses accelerated time to target $C_{average}$ (0.15 µg/mL) but minimally affected steady-state
- Two protocols selected for safety evaluation

Loading doses	Maintenance doses
80 mg BID, 7 days	40 mg BID, 12 weeks
60 mg BID, 7 days	20 mg BID, 12 weeks
40 mg BID, 3 days	20 mg BID, 12 weeks
-	20 mg BID, 12 weeks
40 mg BID, 3 days	16 mg BID, 12 weeks
-	16 mg BID, 12 weeks
40 mg BID, 3 days	12 mg BID, 12 weeks
-	12 mg BID, 12 weeks



Mechanistic Toxicity Parameters of Emvododstat and Its Metabolite Were Estimated Based on In Vitro Data

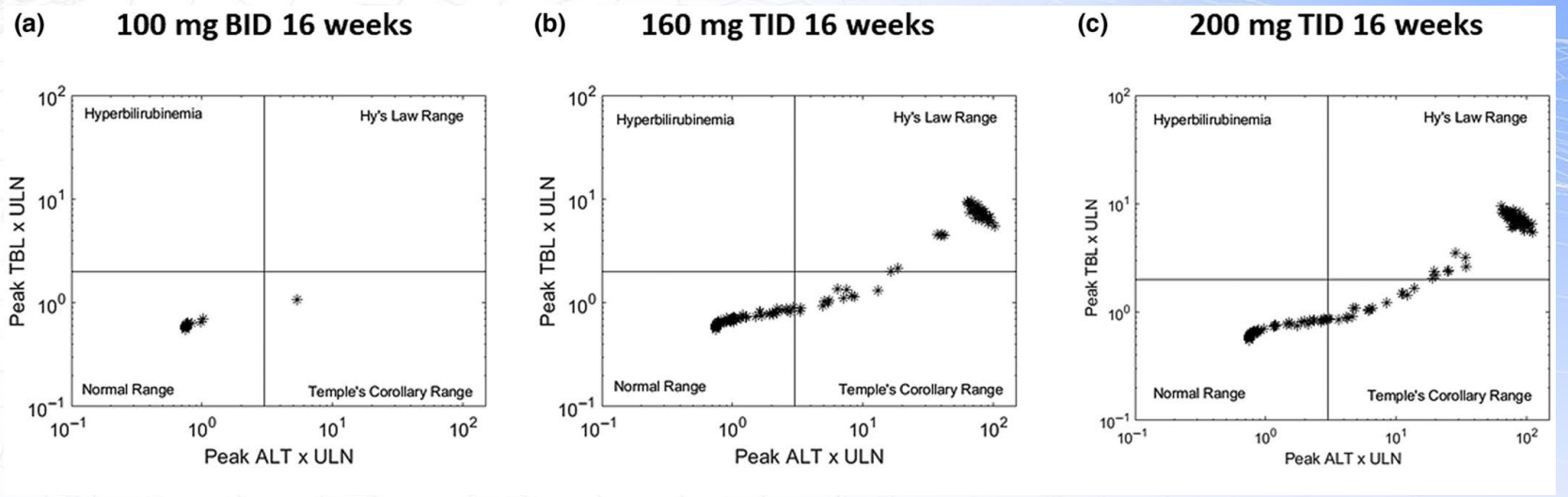
- Emvododstat and O-desmethyl emvododstat had no effect on bile acid transporters
- Emvodostat and O-desmethyl emvododstat acted as weak mitochondrial electron transport chain (ETC) inhibitors
- O-desmethyl emvododstat induced oxidative stress in HepG2 cells

Compound	Mechanism	Parameter	Unit	Value*
Emvododstat	Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	µM	3.5×10^{6}
O-Desmethyl Emvododstat	Oxidative Stress	RNS/ROS production rate constant 1	mL/mol/hr	3×10^{-5}
	Mitochondrial Dysfunction	Coefficient for ETC Inhibition 2	µM	2000
		Coefficient for ETC Inhibition 3	µM	50
		Max inhibitory effect for ETC inhibition 3	Dimensionless	0.4

* Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

DILIsym Correctly Simulated Hepatotoxicity for Retrospective Emvododstat Clinical Protocols

- Dose-dependent DILI predicted for higher dose emvododstat
- Severity over-predicted
  - Clinical stop protocol not included
  - Known adaptive mechanisms (e.g., mitochondrial biogenesis) not included

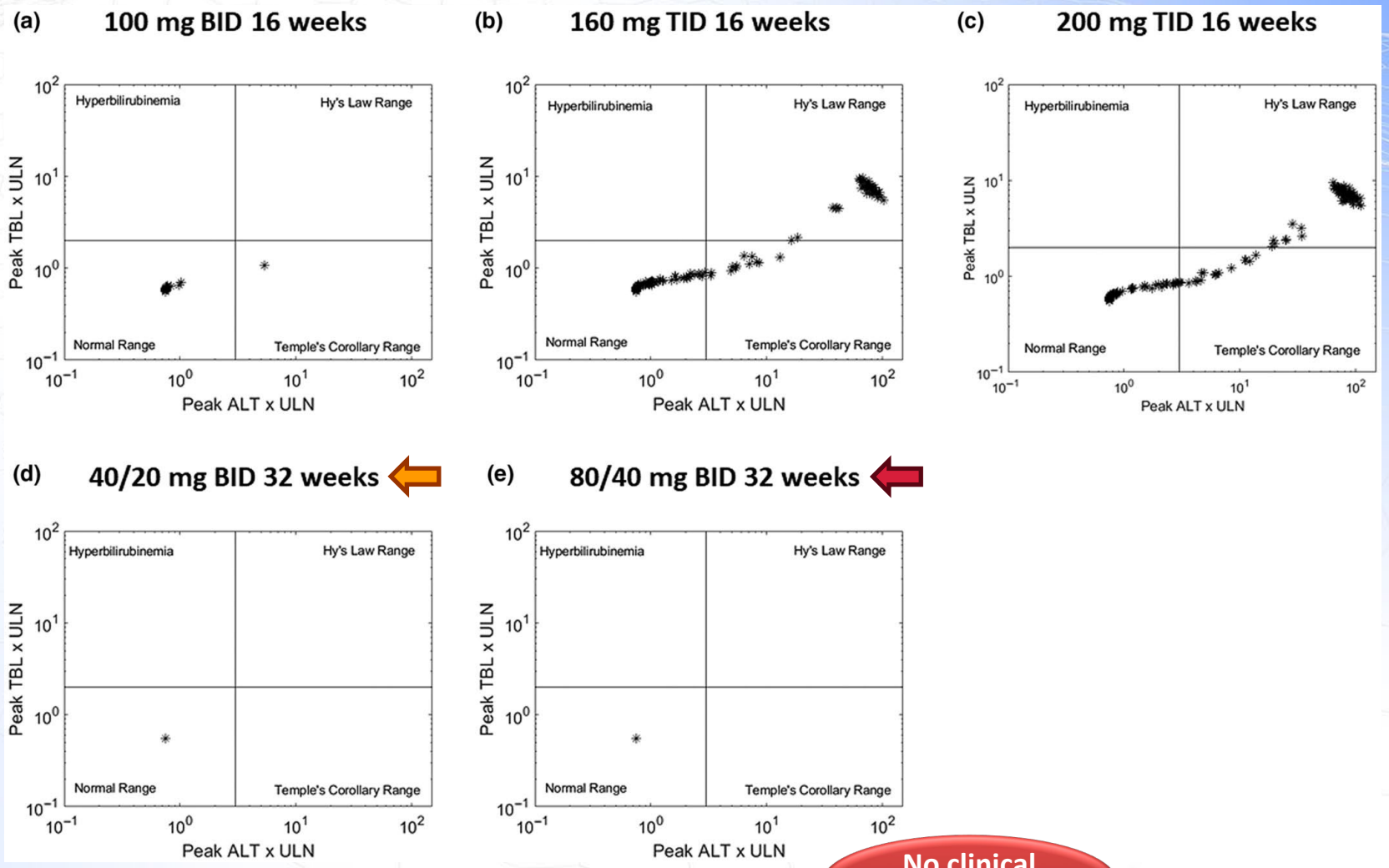


No clinical stop protocol

DILIsym Predicted No Hepatotoxicity for Prospective Emvododstat Clinical Protocols

- Dose-dependent DILI predicted for higher dose emvododstat
- No hepatotoxicity predicted at lower doses targeted for AML patients
  - Even with longer treatment

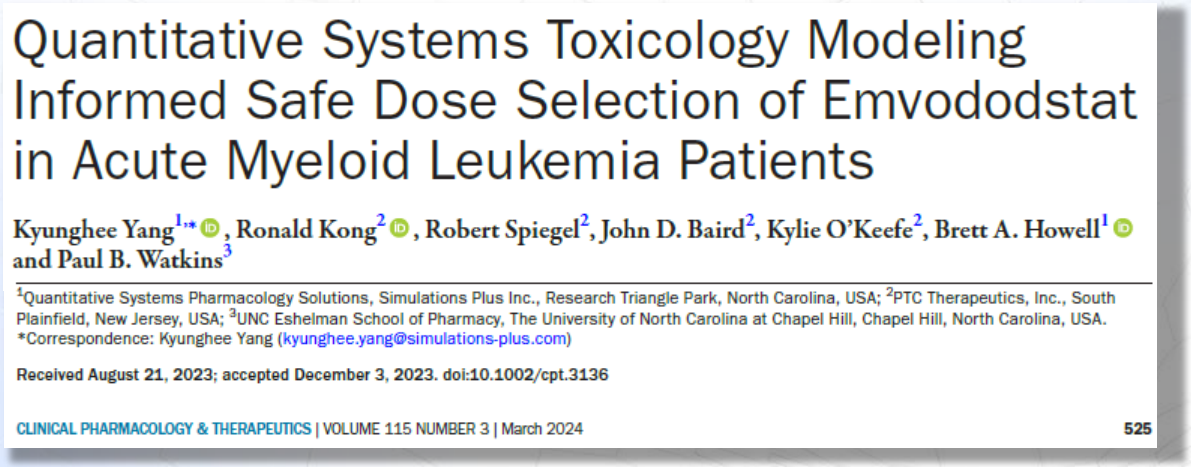
Loading doses	Maintenance doses
80 mg BID, 7 days	40 mg BID, 12 weeks
60 mg BID, 7 days	20 mg BID, 12 weeks
40 mg BID, 3 days	20 mg BID, 12 weeks
-	20 mg BID, 12 weeks
40 mg BID, 3 days	16 mg BID, 12 weeks
-	16 mg BID, 12 weeks
40 mg BID, 3 days	12 mg BID, 12 weeks
-	12 mg BID, 12 weeks



No clinical stop protocol

Prospective DILIsym Simulations of Emvododstat Were Validated with Recent Clinical Trial Results

- **PK exposure and liver safety outcomes from recent clinical trials of Emvododstat are consistent with simulation results, validating DILIsym predictions**
  - Among 33 patients who participated in the AML clinical trial (PTC299-HEM-001-LEU), only 5 patients experienced elevations in AST/ALT, all of which were mild (Grade 1), all resolving within a short period of time and no patient showed symptoms of hepatic toxicity



Quantitative Systems Toxicology Modeling Informed Safe Dose Selection of Emvododstat in Acute Myeloid Leukemia Patients

Kyunghee Yang[1,*], Ronald Kong[2], Robert Spiegel[2], John D. Baird[2], Kylie O'Keefe[2], Brett A. Howell[1] and Paul B. Watkins[3]

[1]Quantitative Systems Pharmacology Solutions, Simulations Plus Inc., Research Triangle Park, North Carolina, USA; [2]PTC Therapeutics, Inc., South Plainfield, New Jersey, USA; [3]UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.
*Correspondence: Kyunghee Yang (kyunghee.yang@simulations-plus.com)

Received August 21, 2023; accepted December 3, 2023. doi:10.1002/cpt.3136

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 115 NUMBER 3 | March 2024 525

Conclusions and Perspectives

- In the emvododstat example, QST modeling was utilized for optimization of dosing regimen to minimize DILI risk
- QST modeling of emvododstat was critical to enabling regulatory approval to proceed with the AML clinical trial wherein the predicted liver safety was confirmed
- QST modeling leveraging mechanistic toxicity data from human-derived *in vitro* models and clinically relevant drug exposure can be employed to evaluate hepatic safety of compounds and inform internal/regulatory decisions

Acknowledgements

- PTC Therapeutics
  - Ronald Kong
  - Pius Maliakal
  - Robert Spiegel
  - John D. Baird
  - Kylie O'Keefe
- UNC
  - Paul Watkins
- Simulations Plus
  - Kyunghee Yang
  - Brett Howell
- DILI-sim Initiative
  - Pre-competitive consortium sponsoring DILIsym development (Abbvie, AstraZeneca, GSK, Kenvue, Merck KGaA)
- DILI-sim Advisory Board
  - Paul Watkins
  - Neil Kaplowitz
  - Frank Sistare
  - Jack Uetrecht
  - Robert Roth
  - David Pisetsky