

# Quantitative Systems Toxicology Modeling Provides Novel Mechanistic Insights into Disease-related Tolvaptan Hepatotoxicity



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Simulations Plus

# Disclosure



Paul B. Watkins:

- Chairs the Scientific Advisory Committee for the DILI-sim Initiative and receives compensation for this
  - No longer has an equity interest in DILIsym Services Inc., a Simulations Plus Company



James J. Beaudoin:

- Was affiliated exclusively with UNC when performing the research projects described in this presentation
- Is currently employed as a Scientist I at DILIsym Services Inc., a Simulations Plus Company

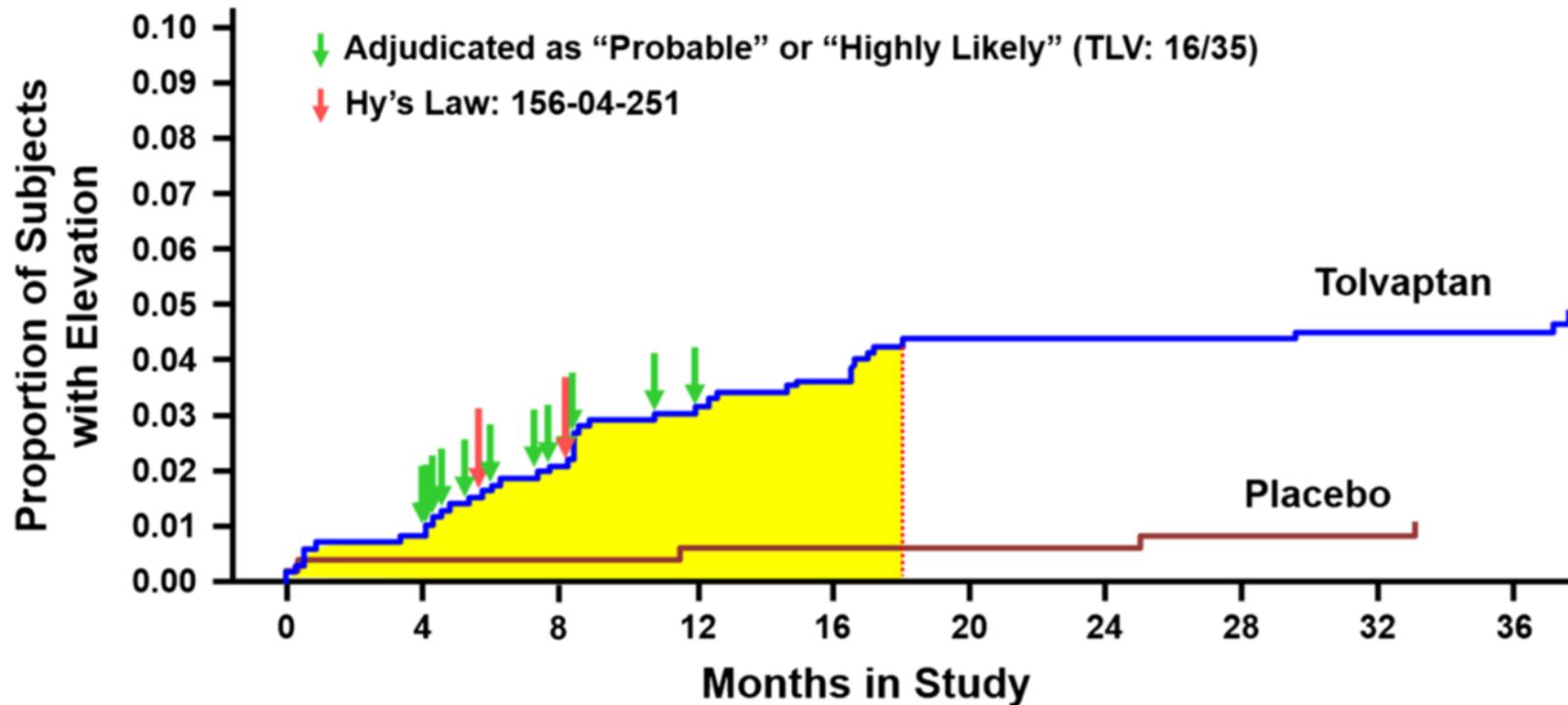
# Tolvaptan Is Approved to Slow Progression of Kidney Cysts in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

## **WARNING: RISK OF SERIOUS LIVER INJURY**

*See full prescribing information for complete boxed warning.*

- **JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported (5.1)**
- **Measure transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter (5.1)**
- **JYNARQUE is available only through a restricted distribution program called the JYNARQUE REMS Program (5.2)**

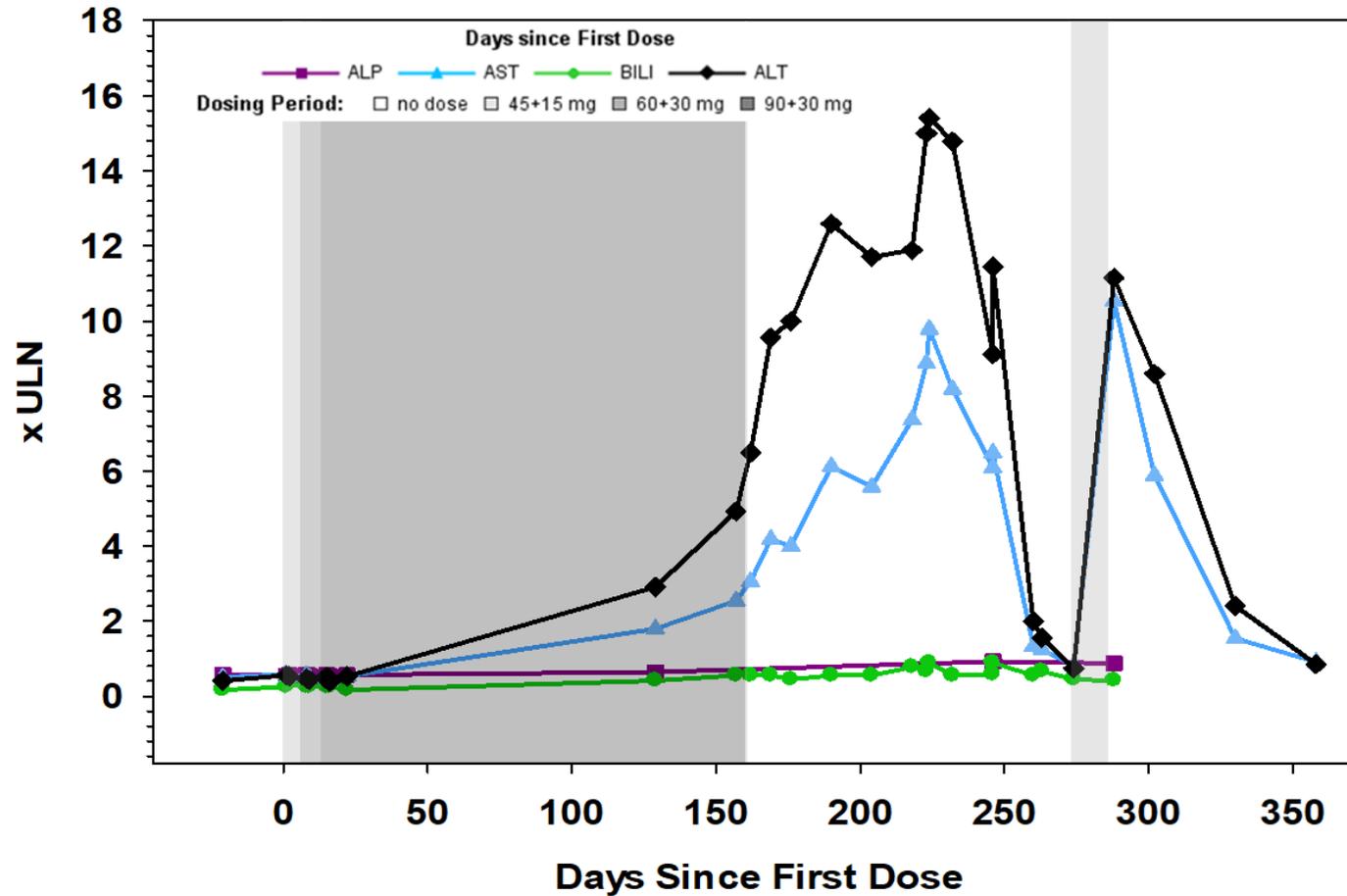
# Incidence of Tolvaptan Hepatotoxicity in Patients with ADPKD



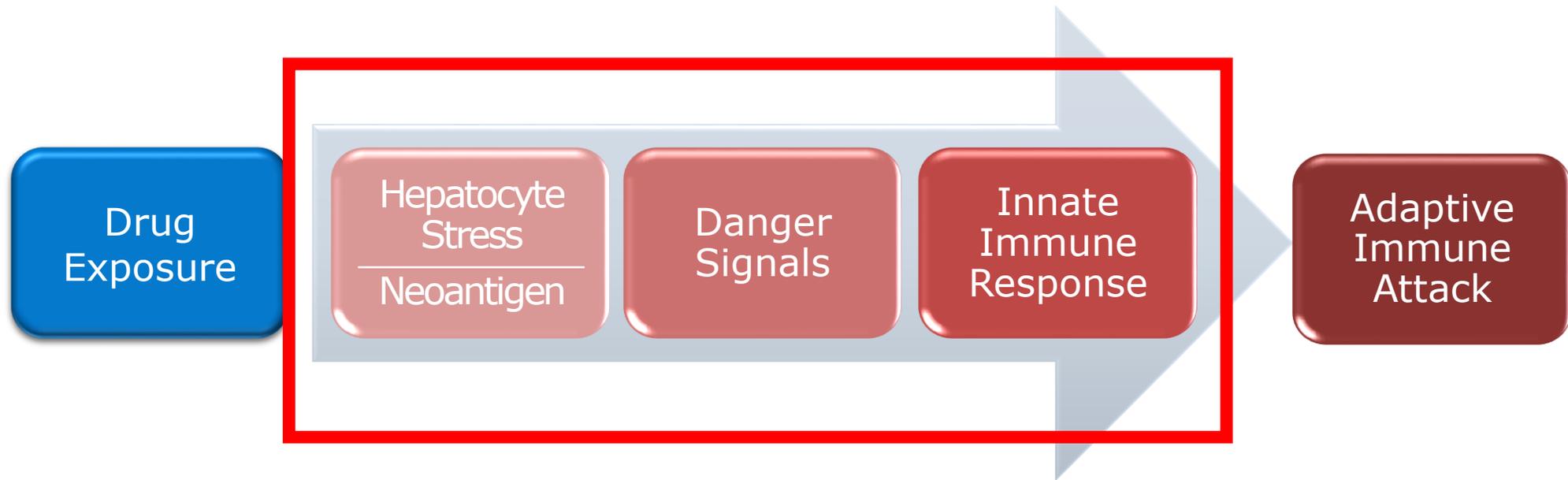
Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	796	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147

ADPKD (Autosomal Dominant Polycystic Kidney Disease)

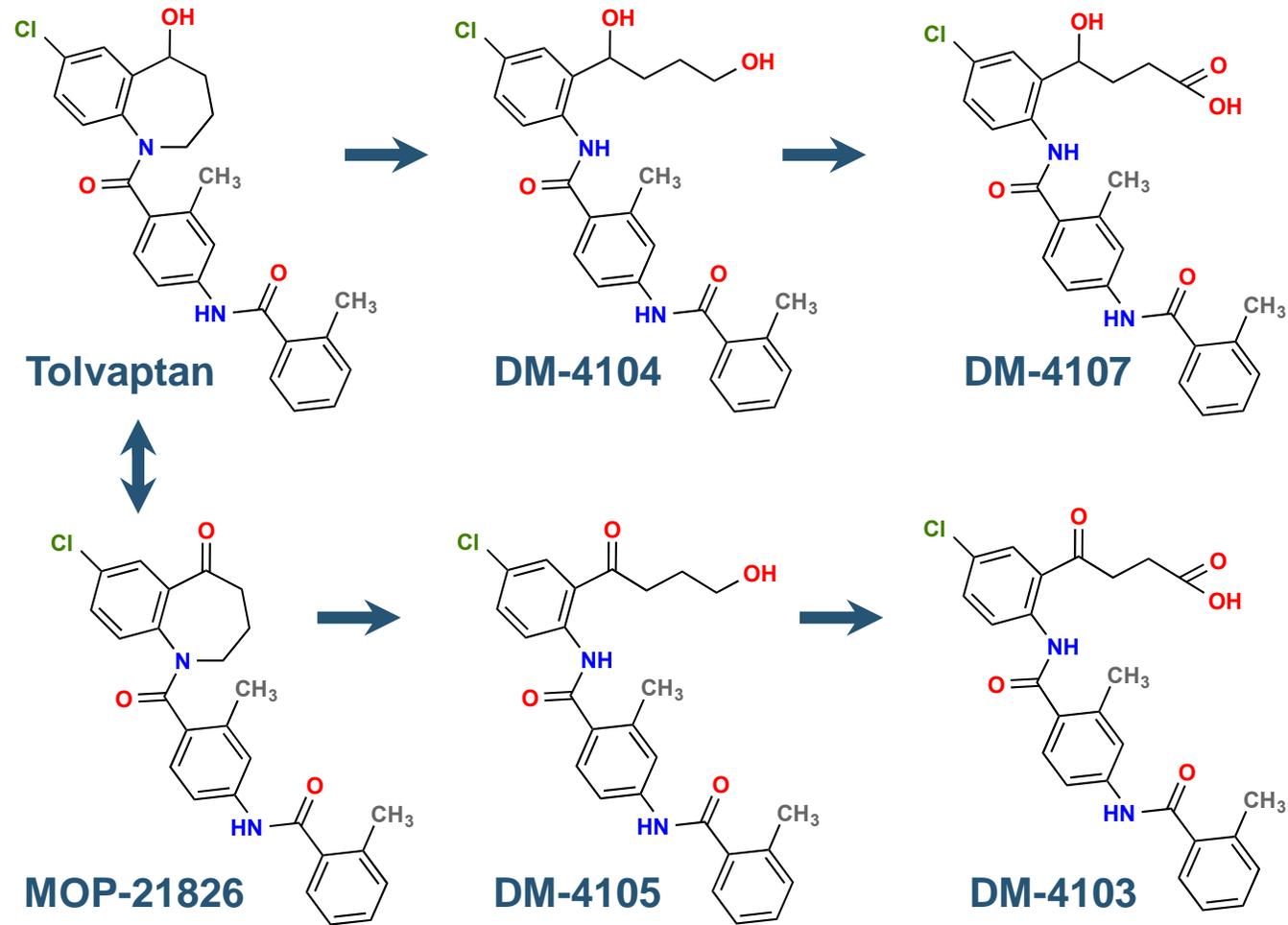
# Case of Tolvaptan Liver Injury with Positive Rechallenge



# Current Concept on Mechanisms Underlying Idiosyncratic Hepatotoxicity of Drugs

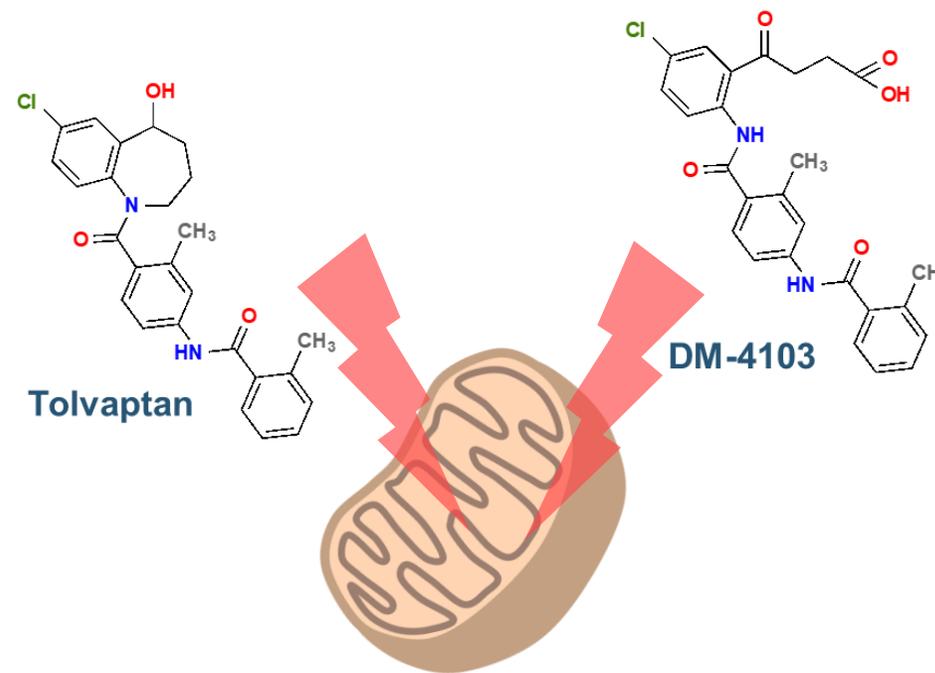


# DM-4103 and DM-4107 Are Two Major Tolvaptan Metabolites



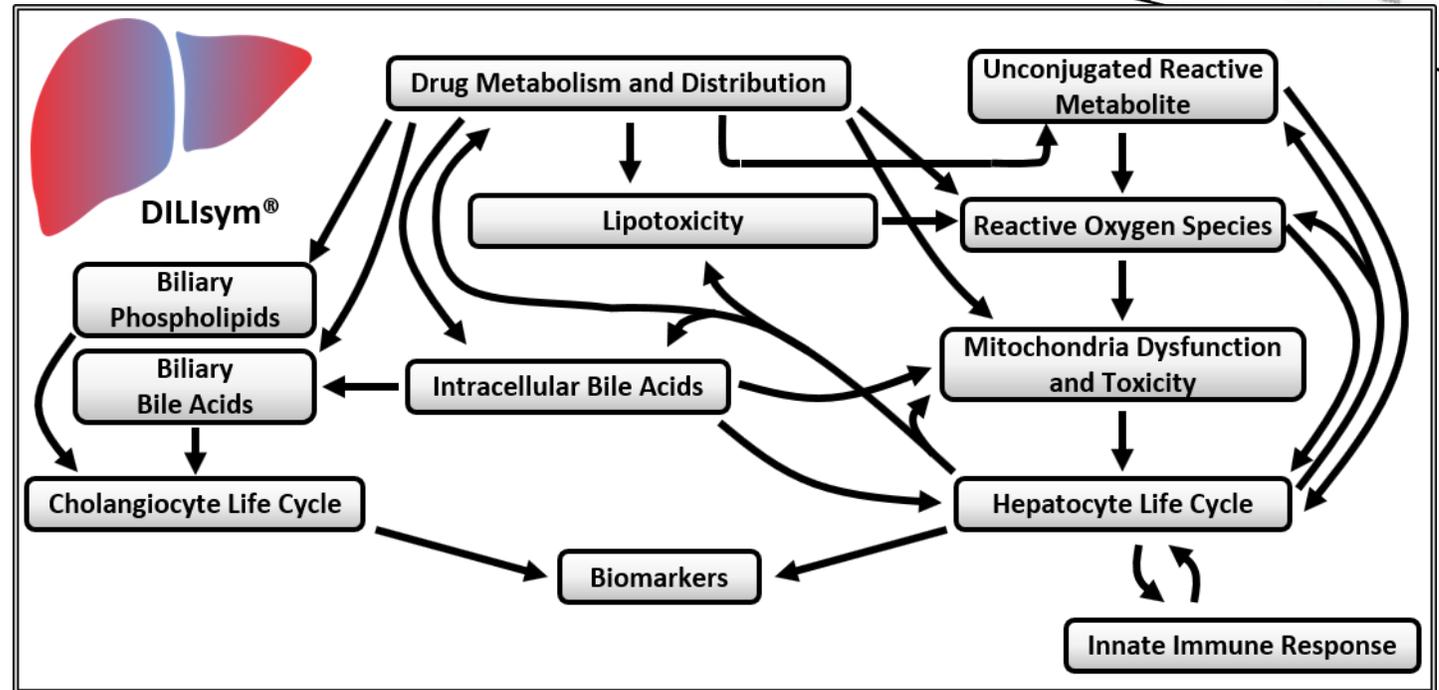
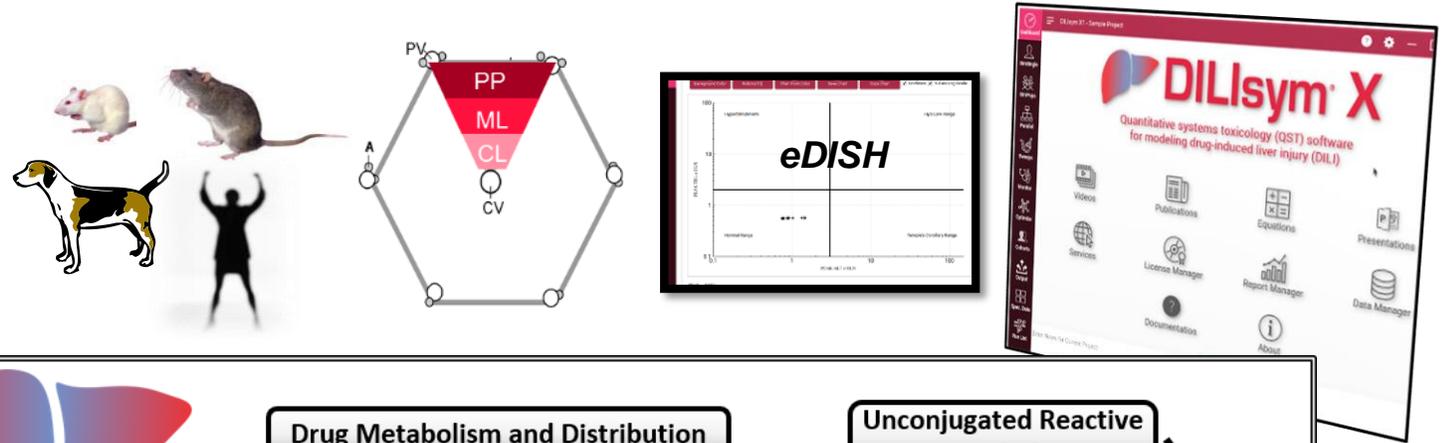
# Tolvaptan and DM-4103 Inhibit Hepatic Bile Acid Transporters and Impair Mitochondrial Respiration

Transporter	Inhibitor	IC <sub>50</sub> (μM)
NTCP	Tolvaptan	~41.5
	DM-4103	16.3
	DM-4107	95.6
BSEP	Tolvaptan	31.6
	DM-4103	4.15
	DM-4107	119
MRP2	Tolvaptan	>50
	DM-4103	~51.0
	DM-4107	>200
MRP3	Tolvaptan	>50
	DM-4103	~44.6
	DM-4107	61.2
MRP4	Tolvaptan	>50
	DM-4103	4.26
	DM-4107	37.9

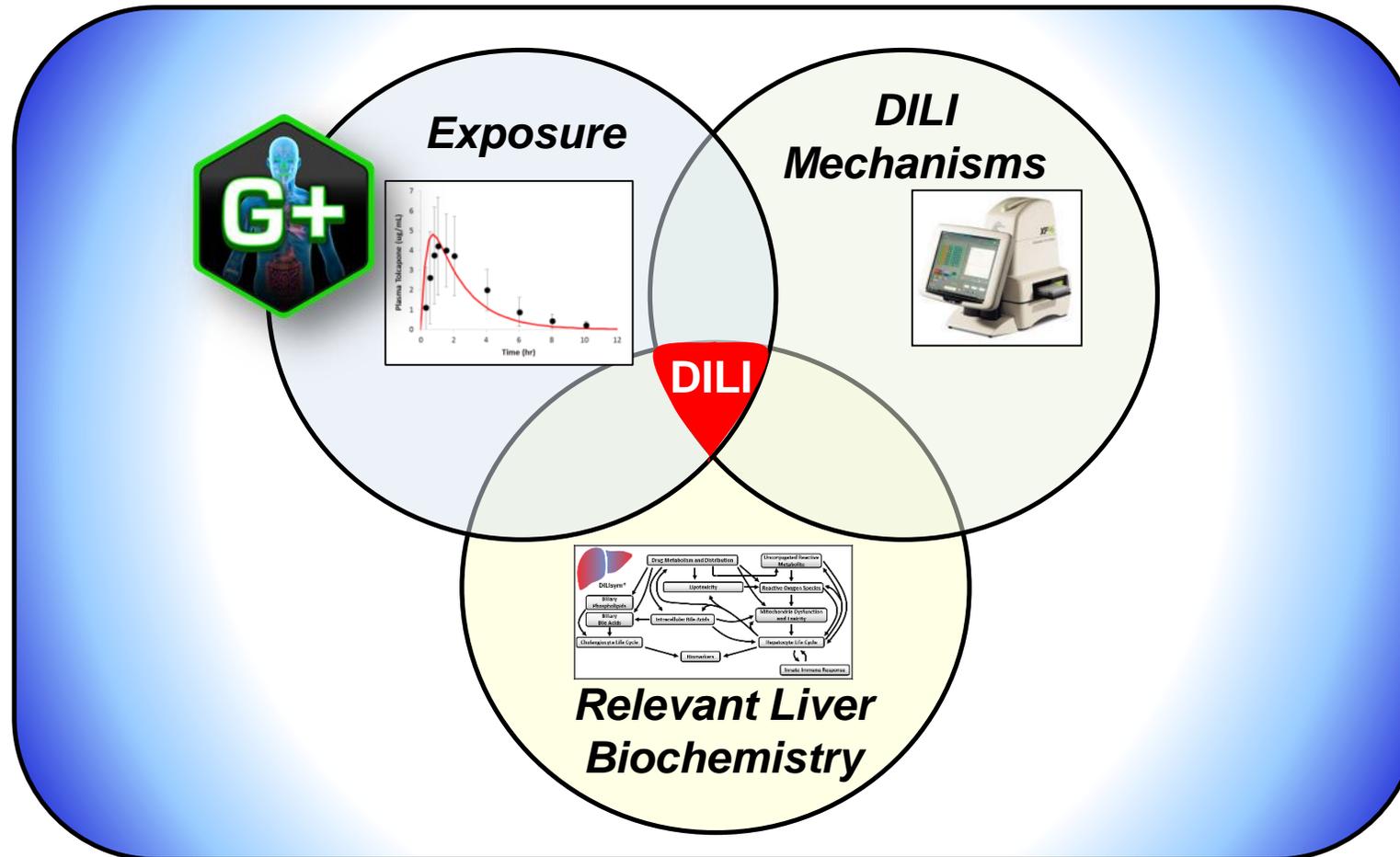


# DILIsym<sup>®</sup> : QST Software Created by the DILI-sim Initiative

- Multiple species: human, rat, mouse, and dog
  - Population variability
- The three primary acinar zones of liver represented
- Essential cellular processes represented to multiple scales in interacting sub-models
- Over 80 detailed representations of optimization or validation compounds with ~80% success
- Single and combination drug therapies



# DILIsym<sup>®</sup> Predicts DILI via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability



# DILIsym<sup>®</sup> Model of Tolvaptan Was Previously Developed and Revealed Dominant Mechanisms for Toxicity

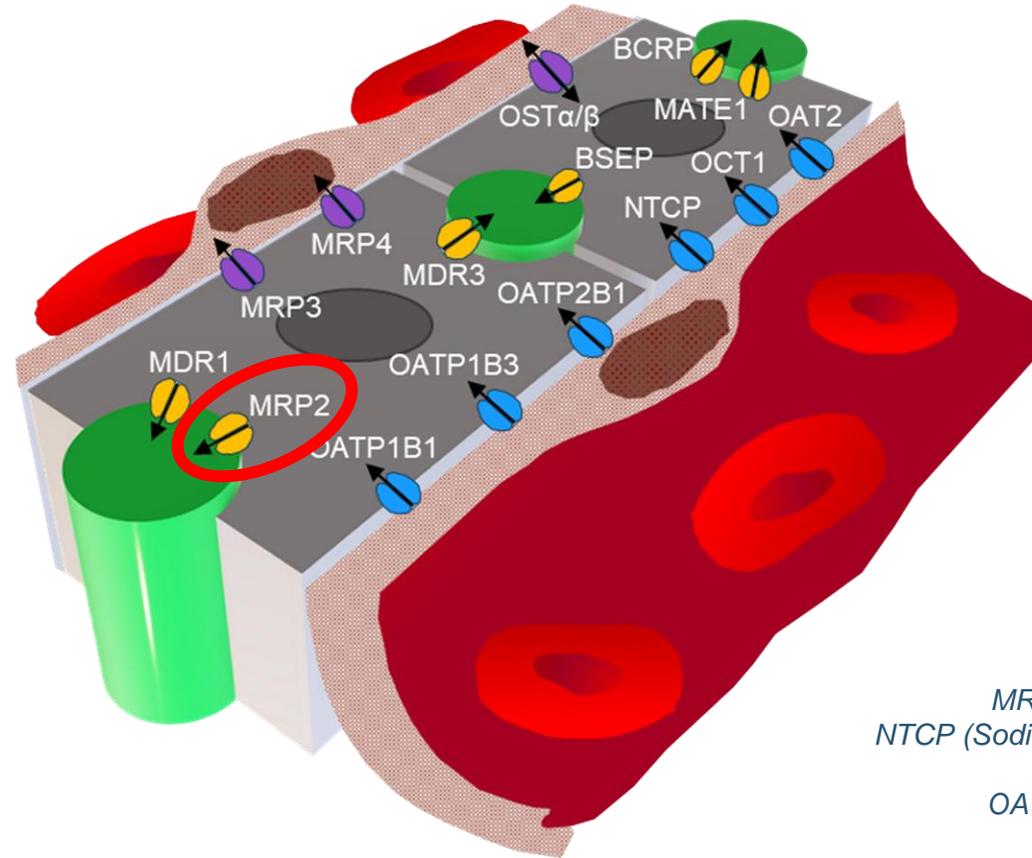
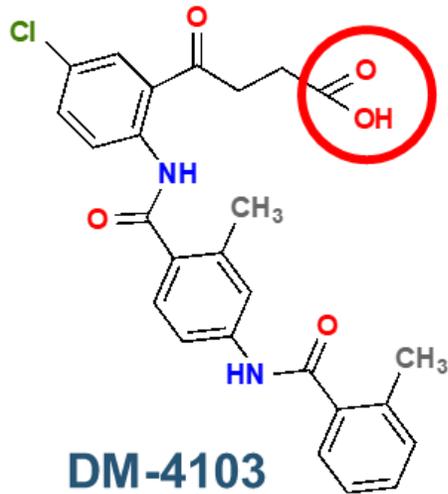
Frequency of Simulated ALT Elevations in a Renally Sufficient SimPops <sup>®</sup>		
Toxicity Mechanisms	Dose	Simulated ALT >3x ULN
All-on	60 mg daily, 60 days	1/229
<b>All-on</b>	<b>90/30 mg daily, 180 days</b>	<b>18/229</b>
Tolvaptan-off	90/30 mg daily, 180 days	0/229
DM-4103-off	90/30 mg daily, 180 days	5/229
ETCi-off	90/30 mg daily, 180 days	9/229
Bile Acids-off	90/30 mg daily, 180 days	0/229

- Previous mechanistic modeling of tolvaptan in DILIsym showed that tolvaptan causes hepatocyte stress primarily by altering bile acid homeostasis
- Tolvaptan metabolite DM-4103 was shown to contribute to the toxicity

ETCi (Electron Transport Chain Inhibition)

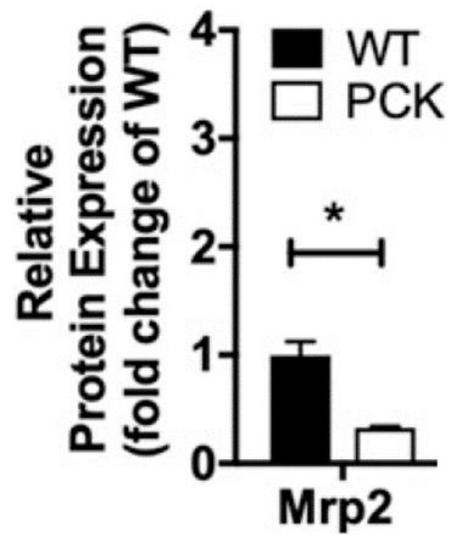
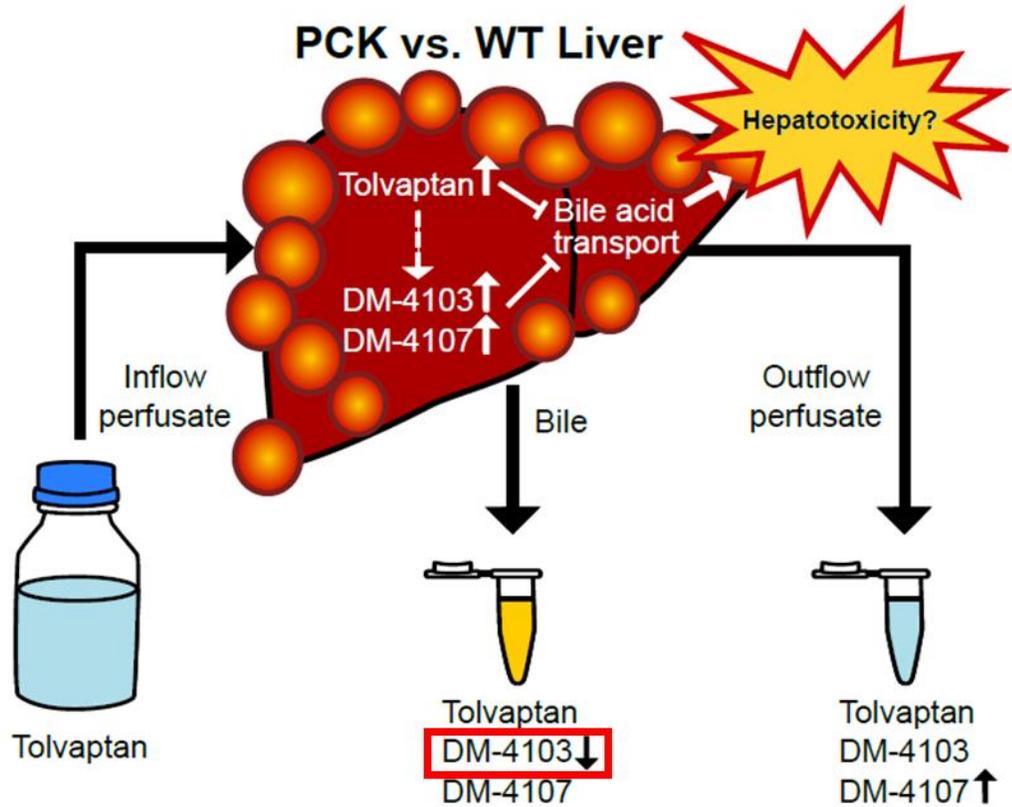
New Insights Suggest a Role for  
**Reduced Biliary Efflux of DM-4103** and **MRP2 Dysfunction**  
in Polycystic Kidney Disease

# MRP2 Is a Biliary Efflux Transporter Expressed by Hepatocytes That Translocates Organic Anionic Compounds into Bile



- BCRP (Breast Cancer Resistance Protein)*
- BSEP (Bile Salt Export Pump)*
- MATE (Multidrug and Toxin Extrusion)*
- MDR (Multidrug Resistance Protein)*
- MRP (Multidrug Resistance-associated Protein)*
- NTCP (Sodium-taurocholate Cotransporting Polypeptide)*
- OAT (Organic Anion Transporter)*
- OATP (Organic Anion Transporting Polypeptide)*
- OCT (Organic Cation Transporter)*
- OSTα/β (Organic Solute Transporter α/β)*

# Biliary Recovery of Tolvaptan Metabolite DM-4103 and Expression of Mrp2 Were Reduced in a Rodent Model of ADPKD



DILIsym<sup>®</sup> was used to answer the question:

Considering these new disease-related insights, what is the impact of **reduced biliary efflux** on tolvaptan-associated hepatotoxicity?

# DILIsym<sup>®</sup> Methods

**Dosing regimen:**

Tolvaptan twice a day: 45/15 mg, 60/30 mg or 90/30 mg for 168 days

**Simulation time:**

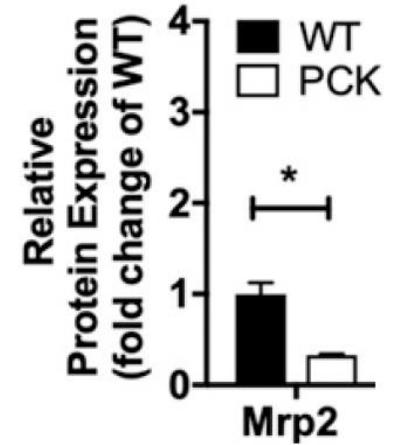
200 days

**Parameters of interest:**

- 1) Tolvaptan's biliary excretion  $V_{max} \rightarrow V_{max,Bile,TVP}$  or  $V_{max,P-gp,TVP}$
- 2) DM-4103's biliary excretion  $V_{max} \rightarrow V_{max,Bile,DM-4103}$  or  $V_{max,MRP2,DM-4103}$

**Baseline human simulations:** Default value, and six  $\log_2$  values below the default value for  $V_{max,Bile,TVP}$ ;  $V_{max,Bile,DM-4103}$

**Virtual population (SimPops) simulations:** Healthy volunteers with variation in 44 parameters

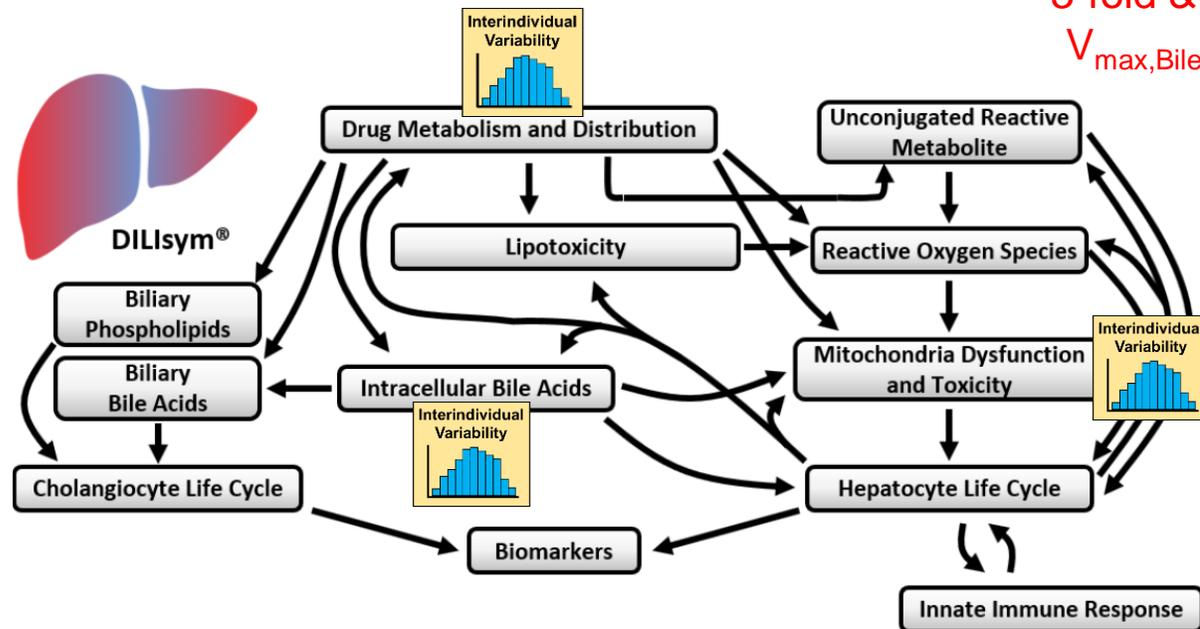


3-fold & 28-fold reductions in  $V_{max,Bile,TVP}$  &  $V_{max,Bile,DM-4103}$



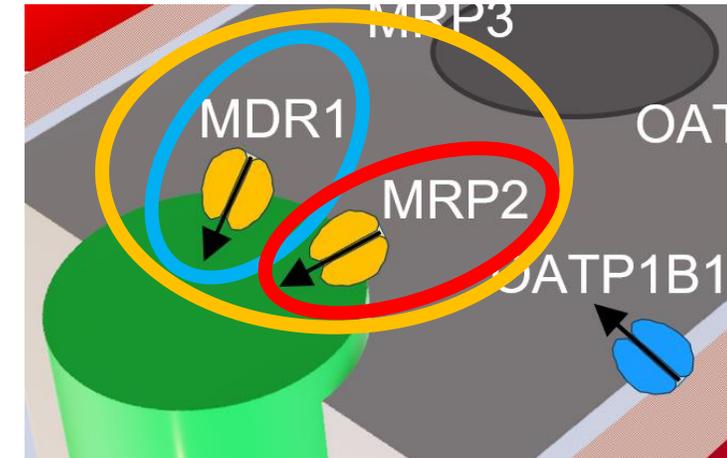
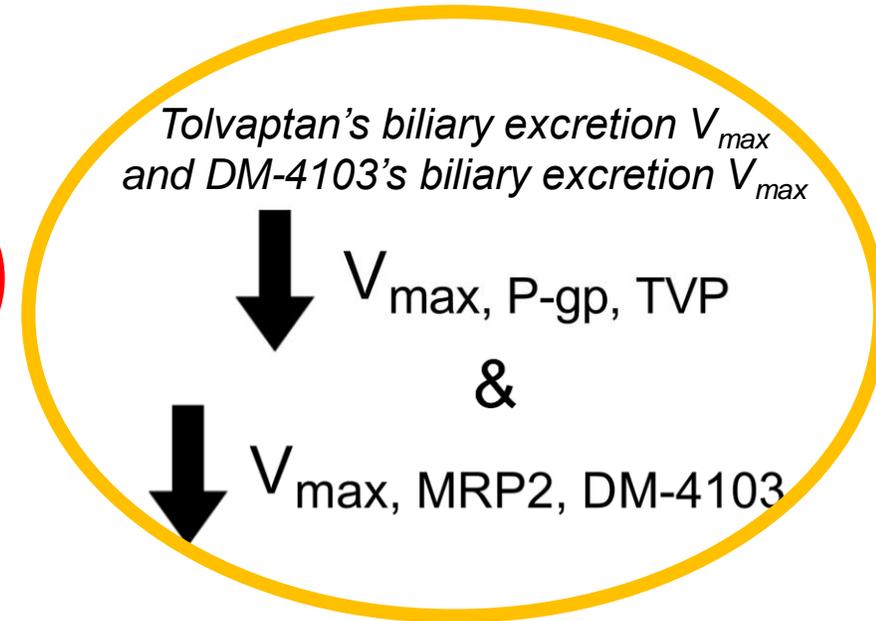
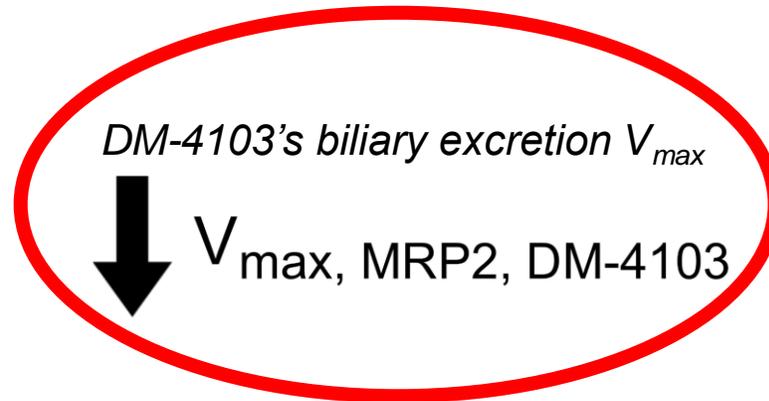
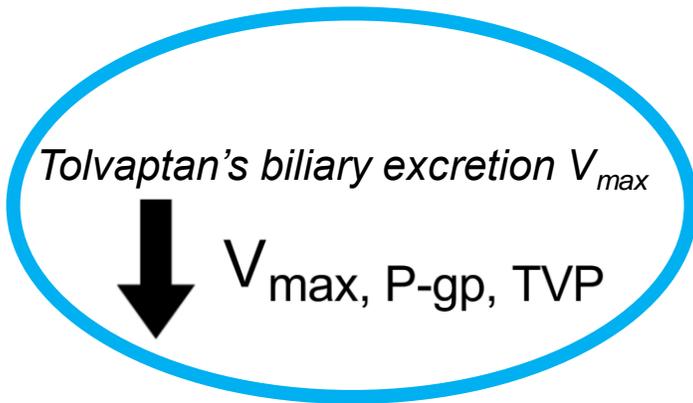
$n = 285$

(Human\_ROS\_apop\_mito\_BA\_v8A\_1)

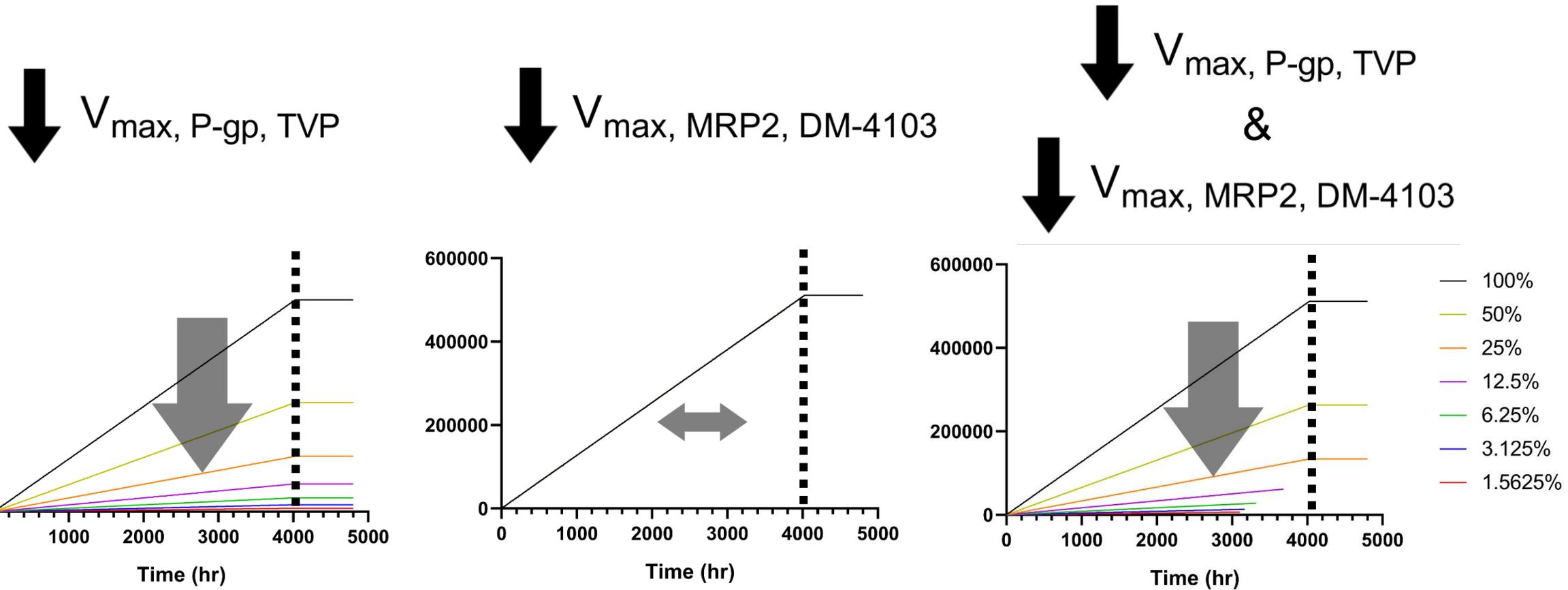


Modified from [www.simulations-plus.com/software/dilisyms](http://www.simulations-plus.com/software/dilisyms)

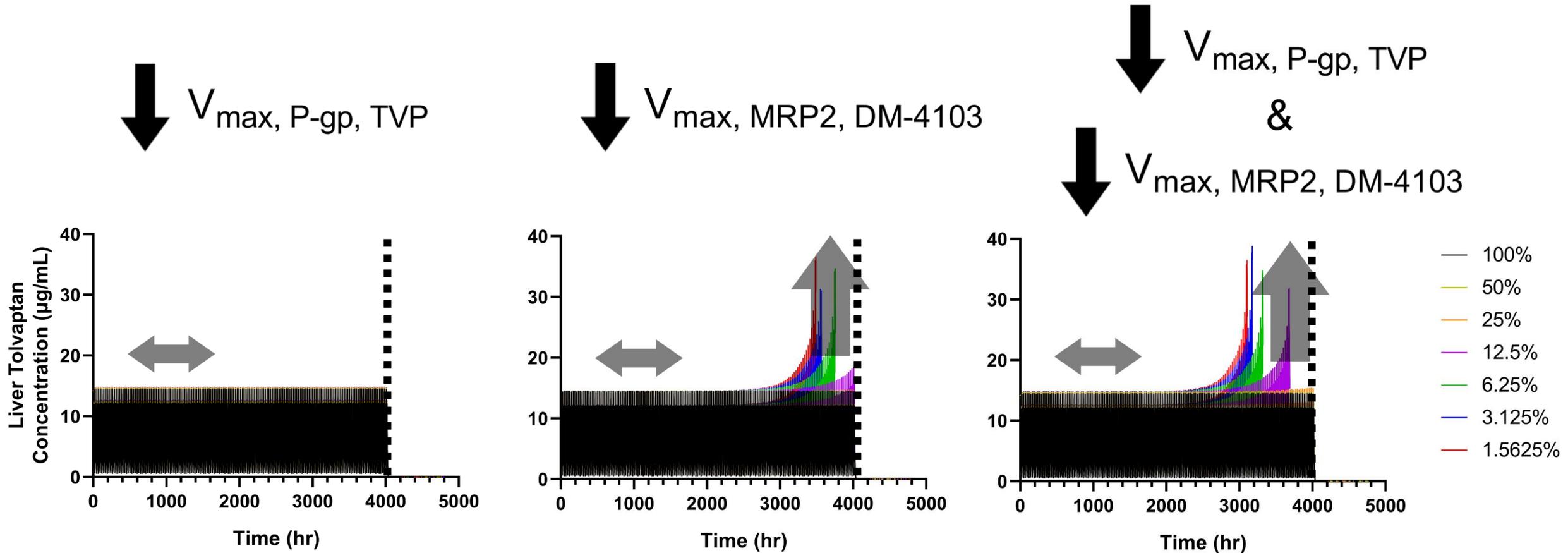
# Sensitivity Analyses in the Baseline Human



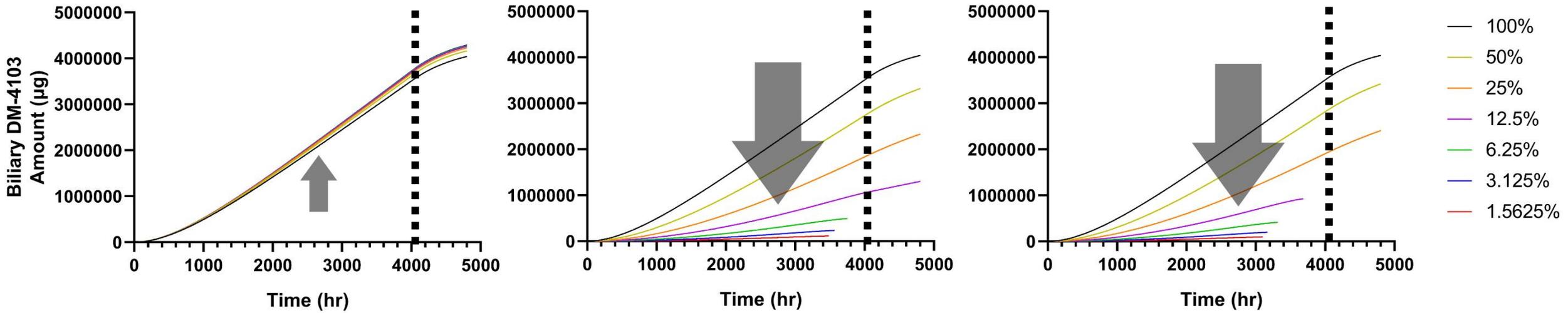
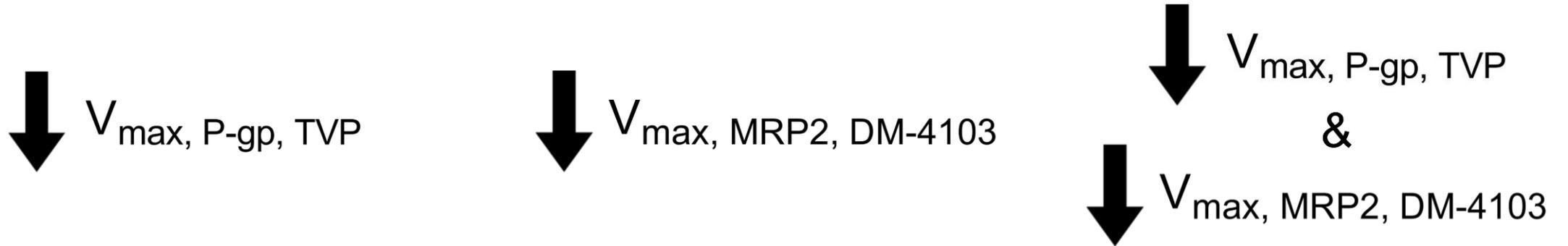
# Biliary Tolvaptan Amounts



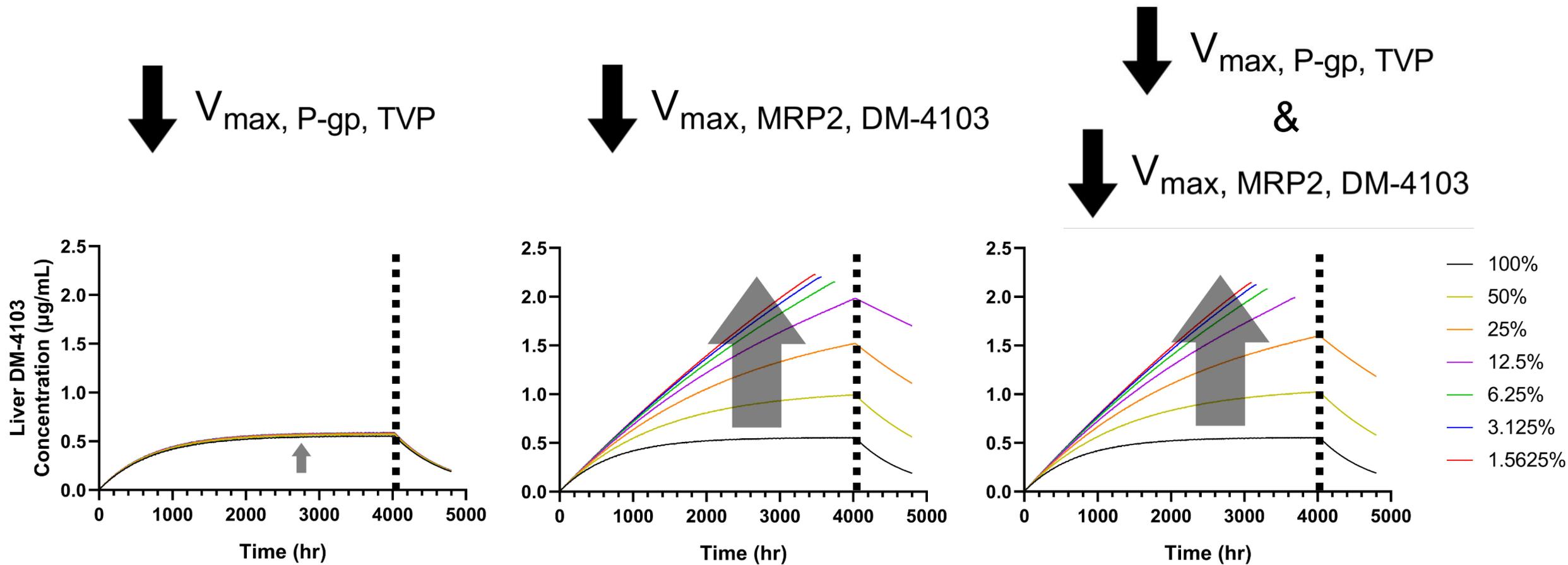
# Hepatic Tolvaptan Concentrations



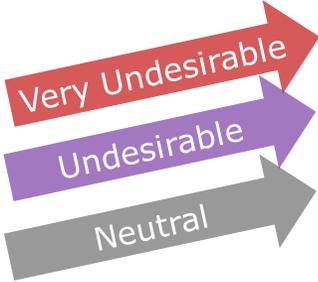
# Biliary DM-4103 Amounts



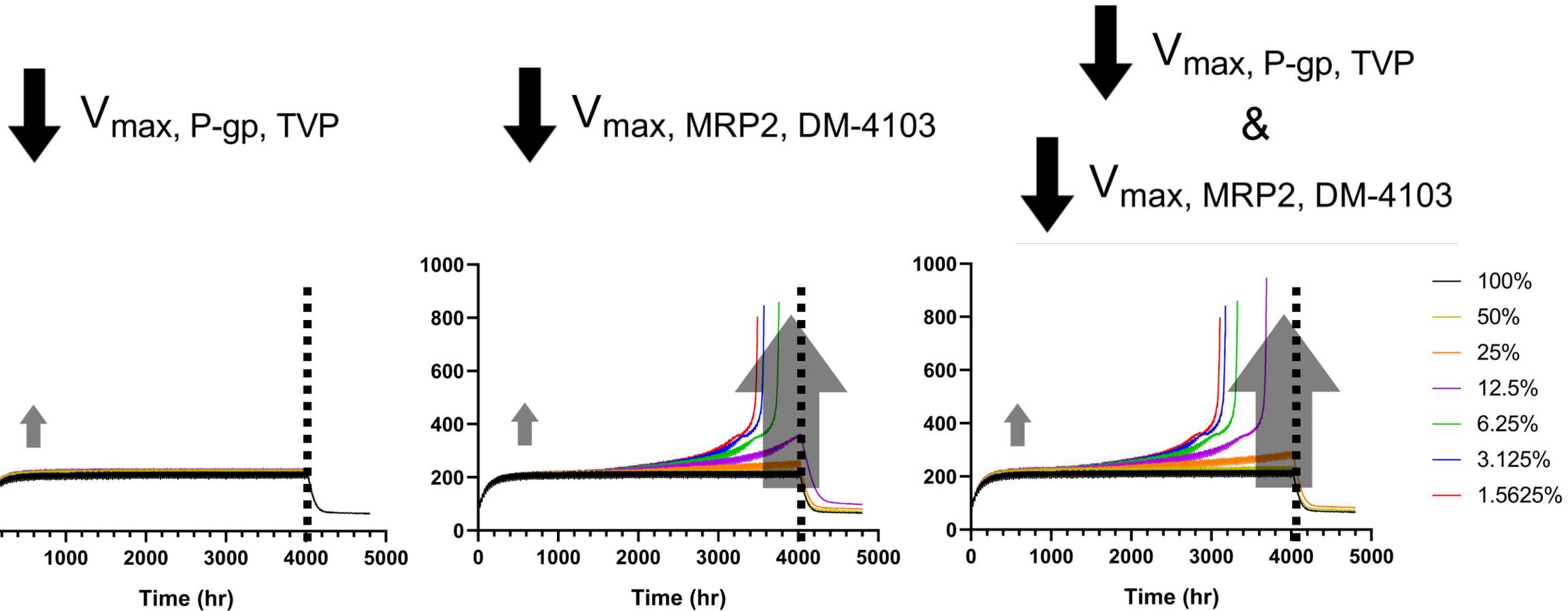
# Hepatic DM-4103 Concentrations



# Summary of DILIsym<sup>®</sup> Pharmacokinetic Simulations After Sensitivity Analyses of Tolvaptan and/or DM-4103 Biliary Excretion $V_{max}$

	↓ $V_{max, P-gp, TVP}$	↓ $V_{max, MRP2, DM-4103}$	↓ $V_{max, P-gp, TVP}$ & ↓ $V_{max, MRP2, DM-4103}$
			
➤ Biliary Tolvaptan Amounts:	↓	↔	↓
➤ Hepatic Tolvaptan Concentrations:	↔	↔ ↑	↔ ↑
➤ Biliary DM-4103 Amounts:	↑	↓	↓
➤ Hepatic DM-4103 Concentrations:	↑	↑	↑

# Hepatic Bile Acid Concentrations

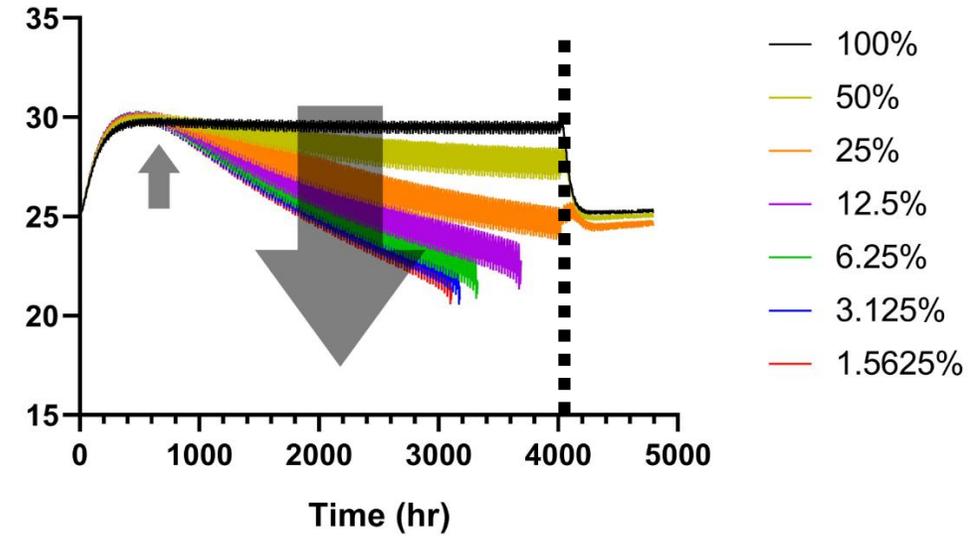
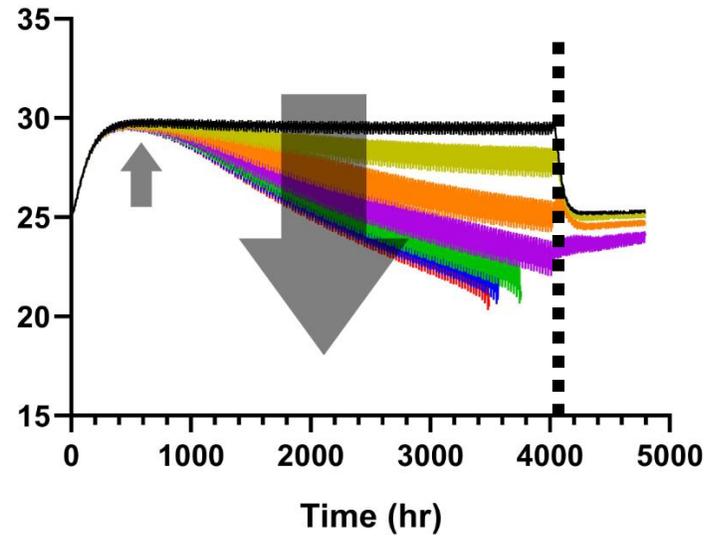
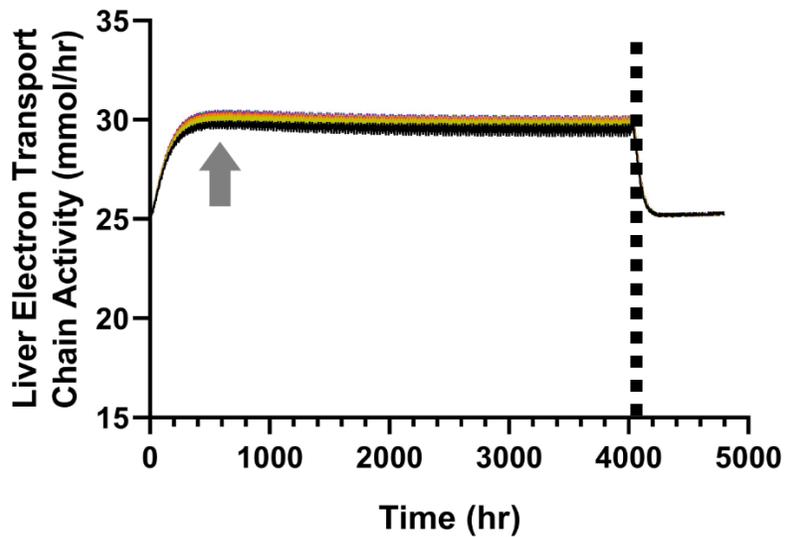


# Hepatic Electron Transport Chain Activity

↓  $V_{\max}$ , P-gp, TVP

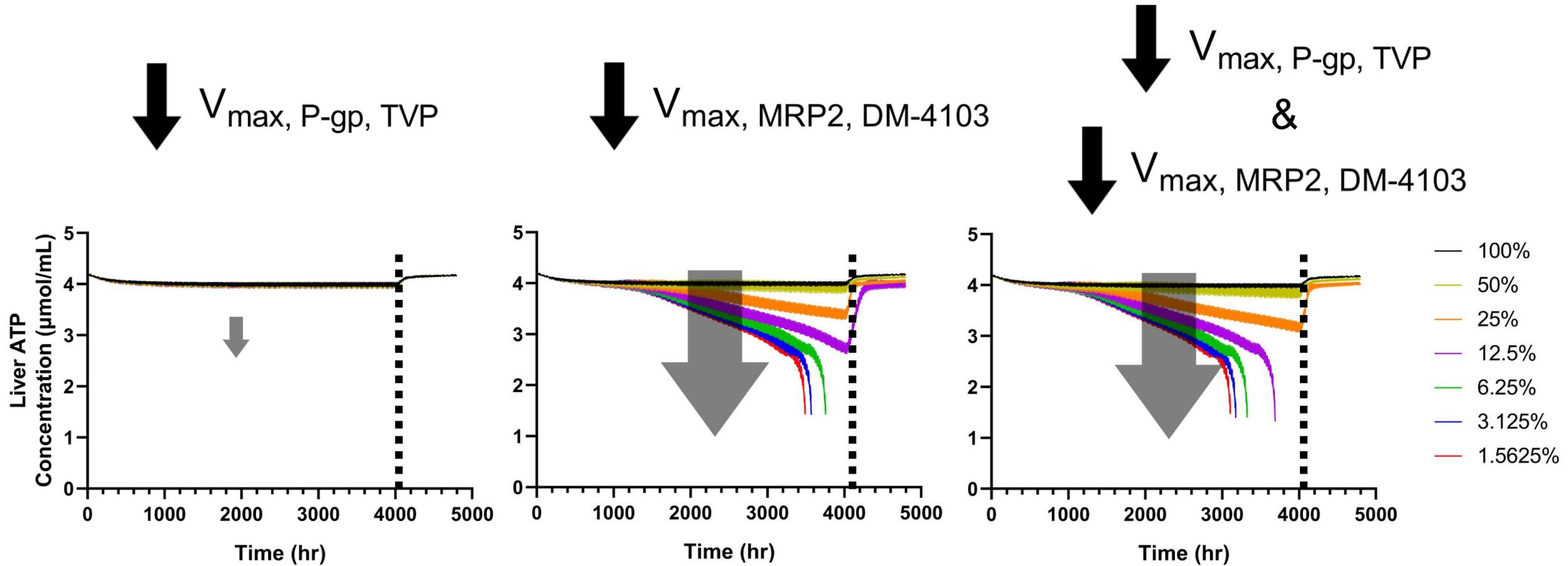
↓  $V_{\max}$ , MRP2, DM-4103

↓  $V_{\max}$ , P-gp, TVP  
&  
↓  $V_{\max}$ , MRP2, DM-4103



- 100%
- 50%
- 25%
- 12.5%
- 6.25%
- 3.125%
- 1.5625%

# Hepatic ATP Concentrations



# Summary of DILIsym<sup>®</sup> Hepatic Bile Acid, ETC and ATP Simulations After Sensitivity Analyses of Tolvaptan and/or DM-4103 Biliary Excretion $V_{max}$

	↓ $V_{max, P-gp, TVP}$	↓ $V_{max, MRP2, DM-4103}$	↓ $V_{max, P-gp, TVP}$ & ↓ $V_{max, MRP2, DM-4103}$
<p>Very Undesirable</p> <p>Undesirable</p> <p>Neutral</p>			
➤ Hepatic Bile Acid Concentrations:	↑	↑ ↑	↑ ↑
➤ Hepatic Electron Transport Chain (ETC) Activity:	↑	↑ ↓	↑ ↓
➤ Hepatic ATP Concentrations:	↓	↓	↓

# Summary of DILIsym<sup>®</sup> Plasma ALT and Total Bilirubin Simulations After Sensitivity Analyses of Tolvaptan and/or DM-4103 Biliary Excretion $V_{max}$

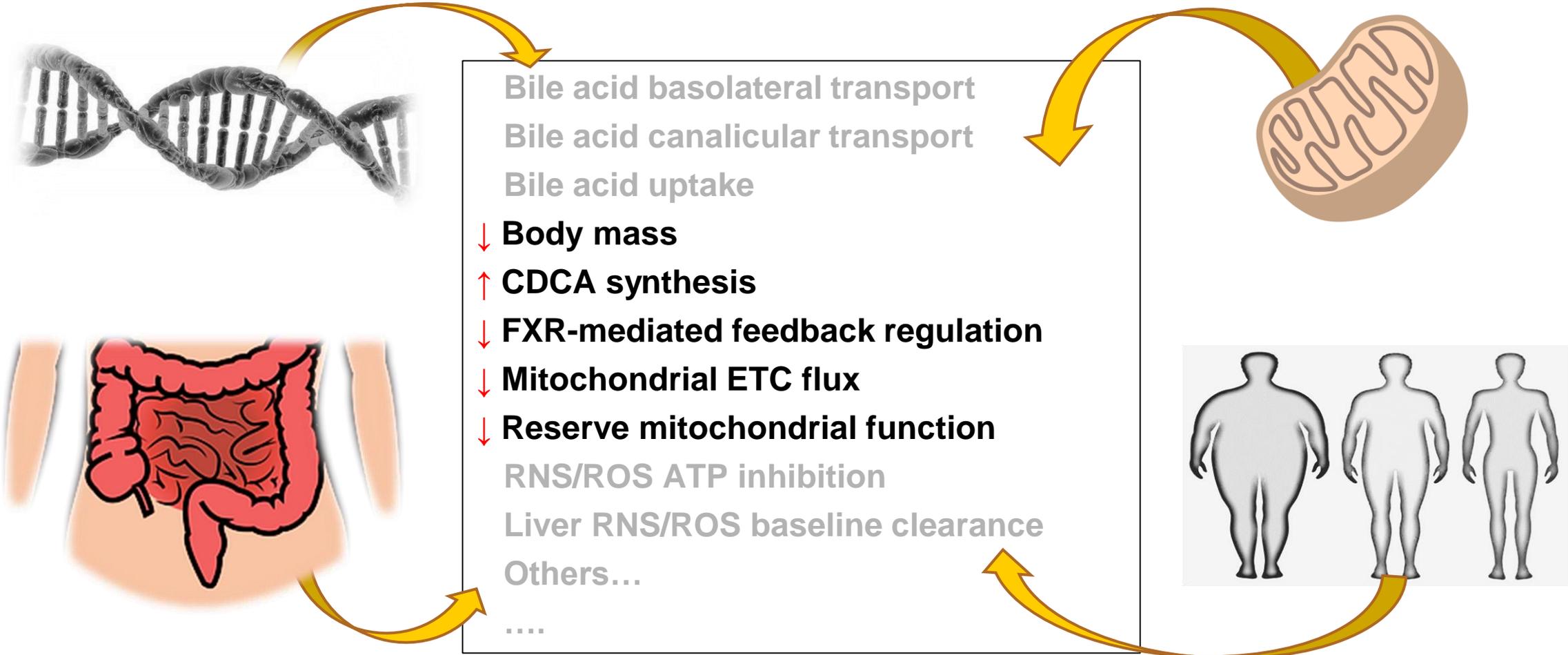
	↓ $V_{max, P-gp, TVP}$	↓ $V_{max, MRP2, DM-4103}$	↓ $V_{max, P-gp, TVP}$ & ↓ $V_{max, MRP2, DM-4103}$
➤ Plasma ALT:	↔	↑	↑
➤ Plasma Total Bilirubin:	↔	↑	↑

# Reduction of the Biliary Excretion of DM-4103 Caused Substantially More Hepatotoxic Events Compared to Tolvaptan

<b>Chemical Species Biliary Excretion <math>V_{max}</math> Altered</b>	<b>Biliary <math>V_{max}</math> Reduction</b>	<b>Simulated ALT &gt;3x ULN</b>
None	N/A	0.35%

Virtual subjects were administered a 90/30 mg daily dose of tolvaptan for 24 weeks.

# A Covariate Analysis Identified Susceptibility Factors of Tolvaptan-associated Hepatotoxicity When Biliary Efflux Was Reduced



# Summary of DILIsym<sup>®</sup> Results

↓  $V_{\max, \text{Bile, TVP}}$

➤ Minor impact

↓  $V_{\max, \text{Bile, DM-4103}}$

- Hepatic accumulation of DM-4103
- Elevated hepatic concentrations of bile acids
- Reduction of hepatic ETC activity
- Reduction of hepatic ATP concentrations

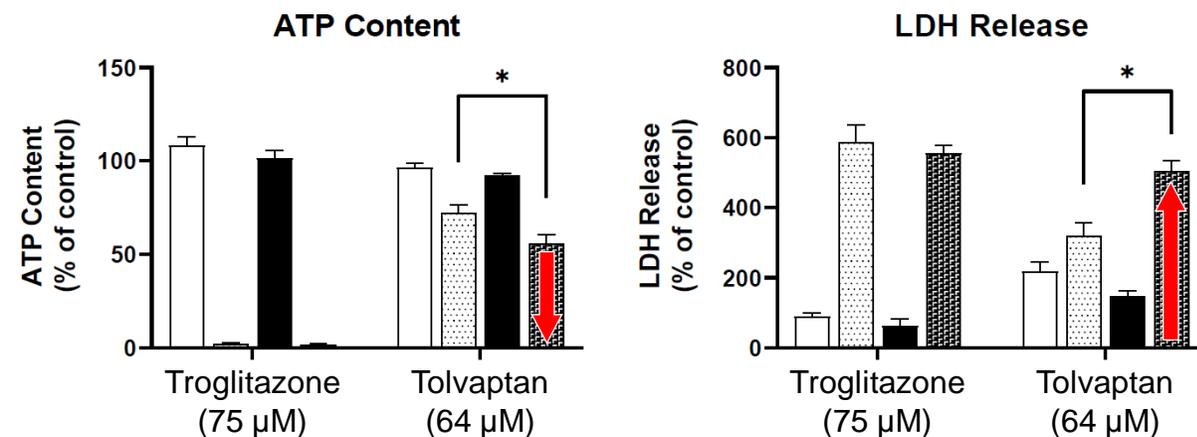
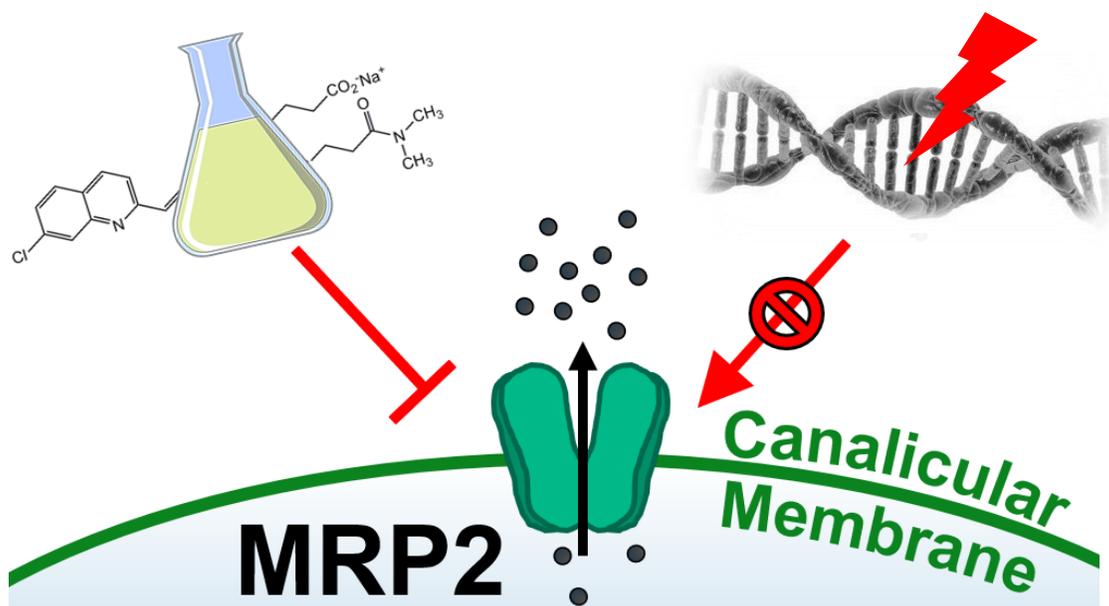
↓  $V_{\max, \text{Bile, TVP}}$

&

↓  $V_{\max, \text{Bile, DM-4103}}$

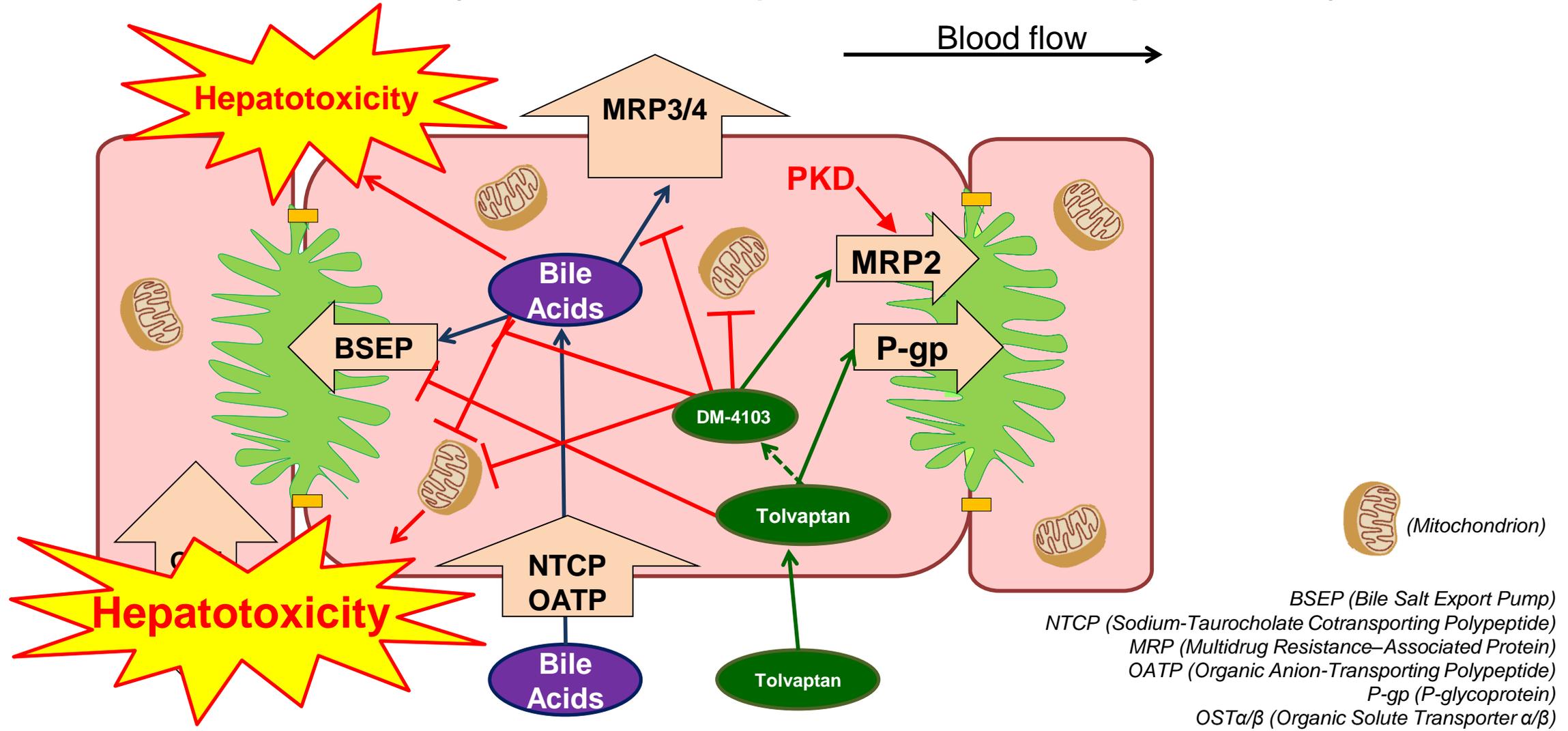
➤ More toxicity than their additive, individual effects

# A Mechanism-based *In Vitro* Assay (C-DILI™) Implicated MRP2 Dysfunction as Key Factor in Susceptibility to Tolvaptan-associated Hepatotoxicity

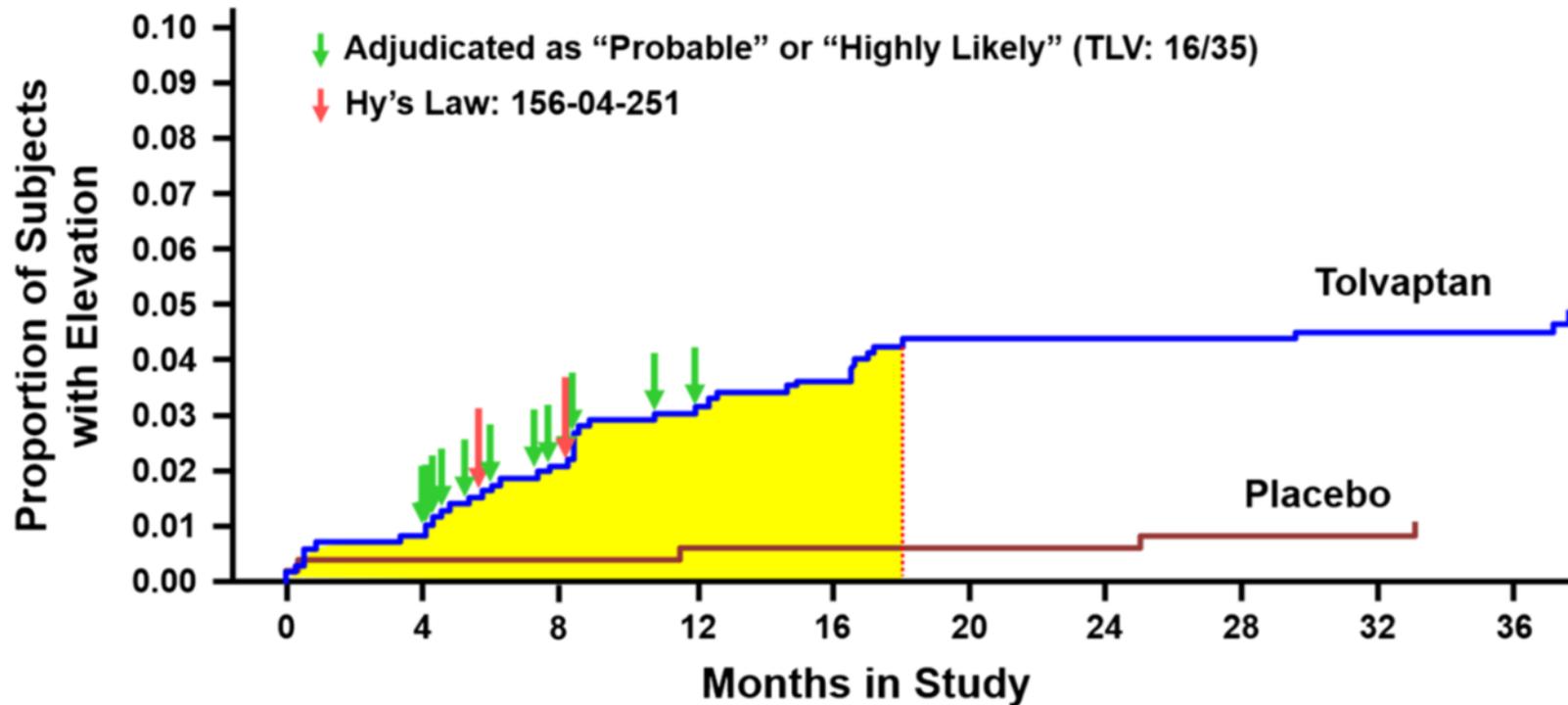


- Control SCHepaRG in Standard Medium
- ▤ Control SCHepaRG in Sensitization Medium
- MRP2<sup>-/-</sup> SCHepaRG in Standard Medium
- ▨ MRP2<sup>-/-</sup> SCHepaRG in Sensitization Medium

# Mechanistic Modeling and *In Vitro* Studies of Drug-induced Liver Injury Suggest a Role for Reduced Biliary Efflux in Tolvaptan-associated Hepatotoxicity

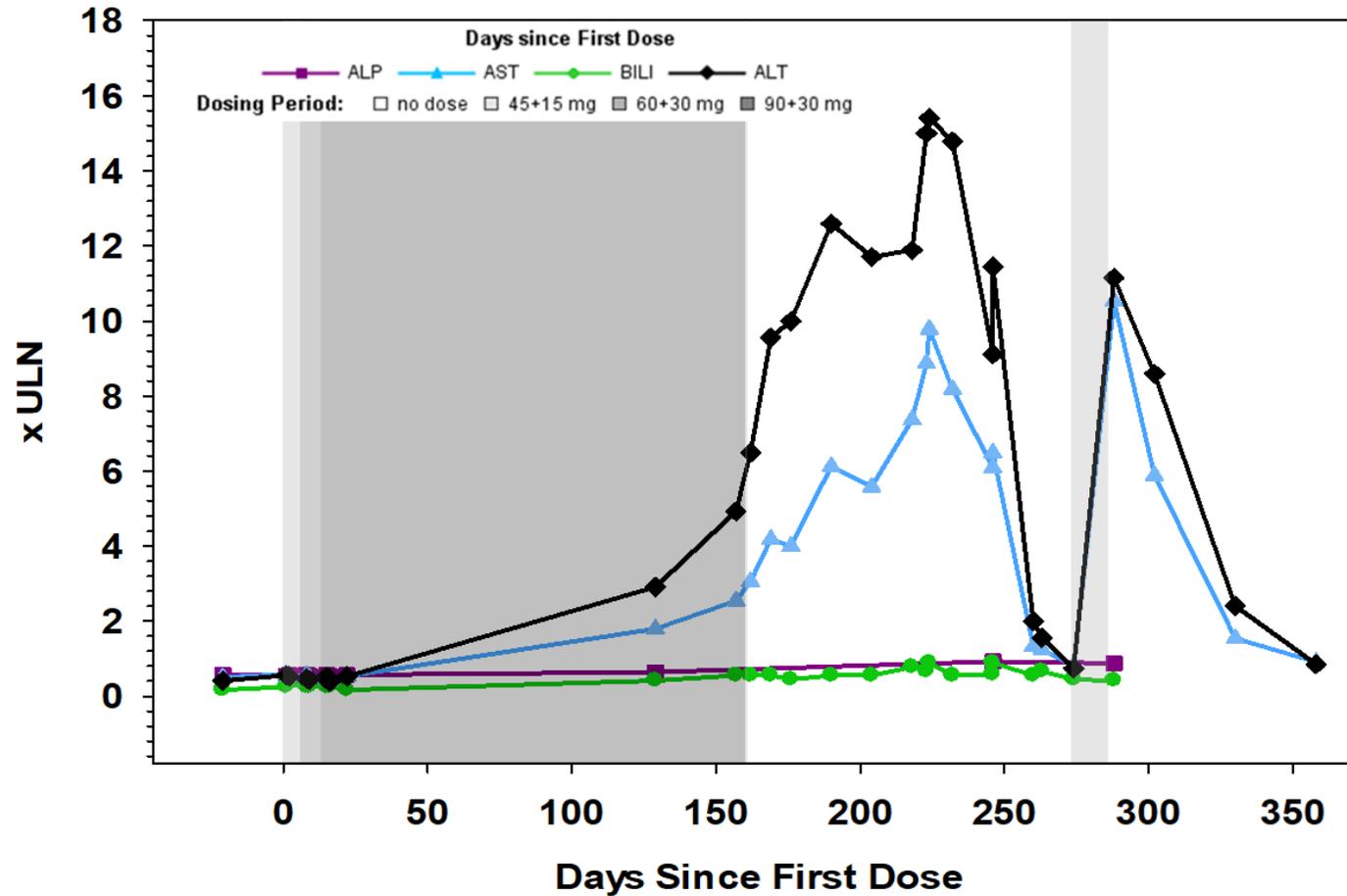


# Disease Progression Could Explain Why Liver Toxicity due to Tolvaptan Occurred After One Year of Treatment

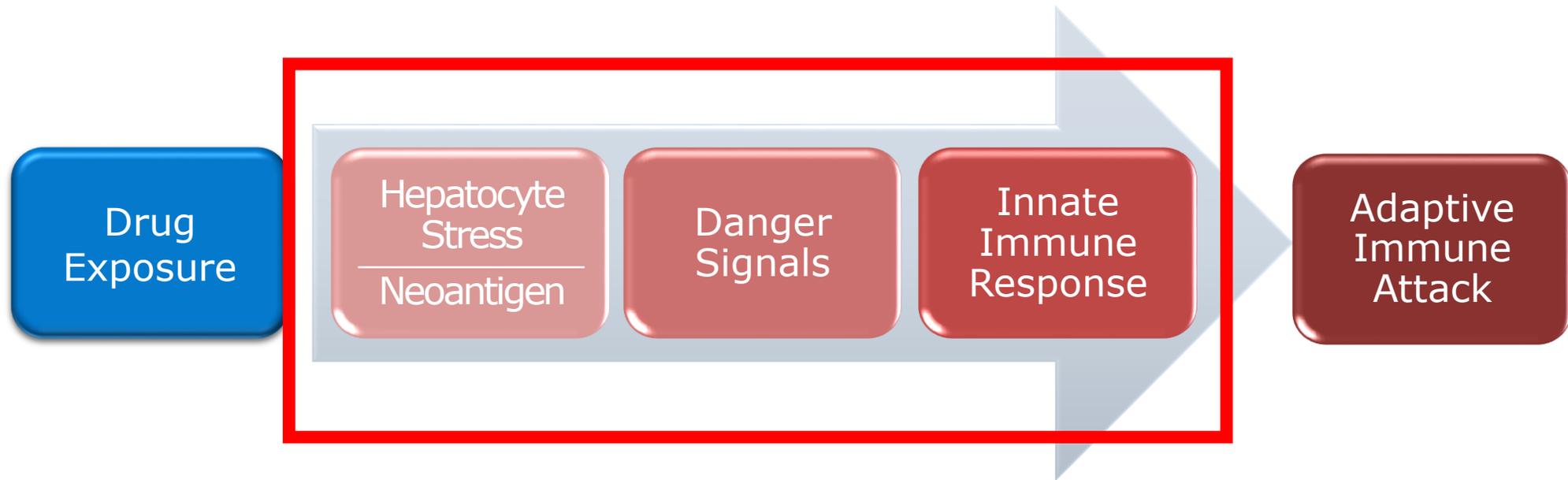


Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	796	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147

# Case of Tolvaptan Liver Injury with Positive Rechallenge



# Current Concept on Mechanisms Underlying Idiosyncratic Hepatotoxicity of Drugs



# Conclusions

- QST and *in vitro* models can provide insights into disease-related mechanisms that contribute to increased DILI risk
- Reduced biliary efflux of DM-4103, likely due to reduced MRP2 activity, may account for increased susceptibility to tolvaptan-associated hepatotoxicity in some patients with ADPKD
- Progression of disease could account for the onset of liver injury after more than one year of tolvaptan treatment