Quantitative Systems Toxicology (QST) Supports Differentiated Liver Safety for a Next-in-Class Compound

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Introduction

Lixivaptan, a vasopressin-2 receptor antagonist, is under development for the treatment of autosomal dominant polycystic kidney disease (ADPKD), an orphan disease with minimal treatment options. Tolvaptan, another vasopressin-2 receptor antagonist, is FDA approved to slow the progression of ADPKD but has produced liver safety signals. We prospectively compared the potential for lixivaptan versus tolvaptan to cause liver toxicity.

Methods

The potential toxicity of lixivaptan and its major metabolites were evaluated in DILIsym, a QST software for predicting drug-induced liver injury. DILIsym integrates:

- In vitro data on lixivaptan-induced oxidative stress, mitochondrial dysfunction, and inhibition of bile acid transporters
- Clinical PK data
- Interindividual variability

Lixivaptan simulation results compared with previously published tolvaptan simulation results (1).

Conclusions

- Lixivaptan was predicted to have an improved liver safety profile relative to tolvaptan for the mechanisms investigated in DILIsym.
- Simulations characterize separation between intended exposure levels and exposure levels associated with ALT elevations.
- **In April 2018, the FDA approved a phase 2 clinical trial for lixivaptan in patients with ADPKD**. Patient enrollment is ongoing.

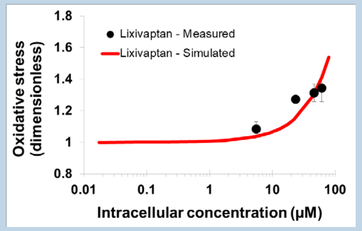
Acknowledgements

- Palladio Biosciences, Inc.
- The members of the DILI-sim Initiative

(1) Woodhead et al., 2017, Toxicol. Sci. *(2) Watkins et al., 2015, Drug Safety*

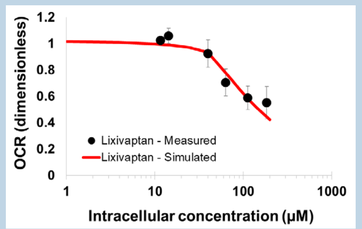
Parameterization using *in vitro* data

Oxidative Stress

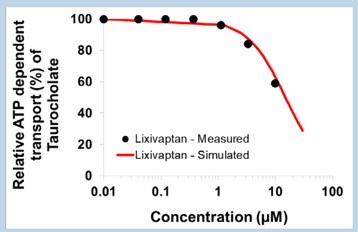


- DILIsym parameter values identified from in vitro data
- Illustrative fits shown
- Complete set of DILIsym input parameter values shown below

Mitochondrial dysfunction



BSEP inhibition



Toxicity parameter values for lixivaptan and major metabolites

Mechanism	DILIsym Parameter	Unit	Value***			
			Lixivaptan	WAY-138451	WAY-141624	WAY-138758
Mitochondrial Dysfunction	Coefficient for ETC inhibition	μM	535	250	N/A	N/A
Oxidative Stress	RNS/ROS production rate constant	mL/nmol/hr	5.45×10^{-4}	2.12×10^{-3}	N/A	N/A
Bile Acid Transporter Inhibition	BSEP inhibition constant	μM	15*	8.6*	39.5*	5.6*
	NTCP inhibition constant	μM	19*	N/A	85.8*	8.9*
	Basolateral inhibition constant**	μM	70*	54*	16.3*	4*

*IC_{50} values; default assumption is mixed inhibition type with $\alpha = 5$, based on the authors' experience.
**Basolateral inhibition constant represents the lowest IC_{50} of the experimentally derived MRP3 and MRP4 IC_{50} values.
***Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications. Their predictive value resides in the combination with exposure in the context of a DILIsym simulation.

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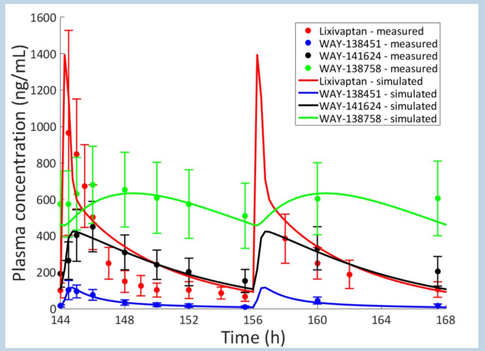
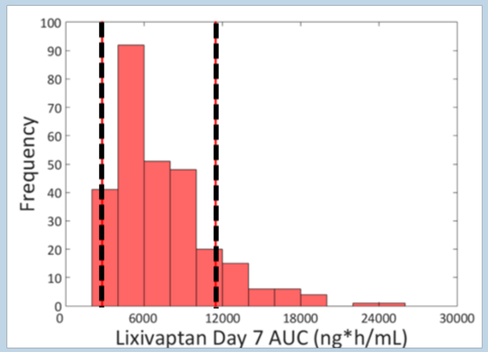
PBPK Parameterization using clinical PK data



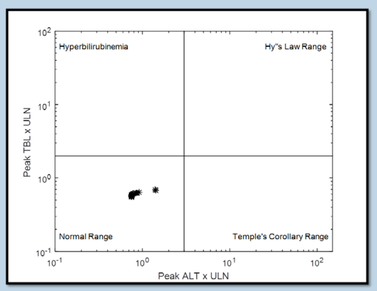
The PBPK representation for lixivaptan and its metabolites was constructed with clinical data from Phase I trial results (n = 67) for seven-day 100 mg BID and 400 mg BID dosing regimens. Simulated liver concentrations consistent with rat WBAR data and in vitro intracellular measurements.

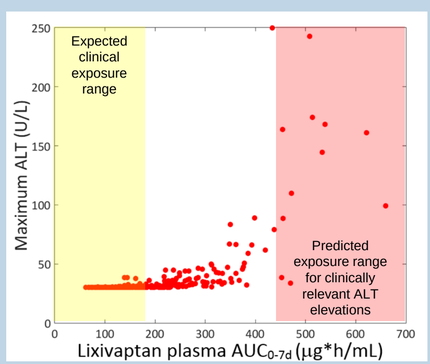


A customized simulated population (SimPops) was created and validated against the observed exposure range for lixivaptan (shown left) and 3 major metabolites. The observed range was reproduced. Outliers were permitted given the larger size of the SimPops (n = 285) and the interest in screening for infrequent safety events.

Results

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





- Simulations predict no clinically significant ALT elevations with lixivaptan
  - Contrasts with simulated and observed tolvaptan ALT elevations (1, 2)
  - Difference in simulation time (12 *vs*. 24 weeks) did not account for difference (results not shown)
- Intended clinical dose falls below exposure range for simulated ALT elevations
  - Lixivaptan simulations with 400 mg, BID for 7 days predicts a correlation between exposure and response
  - Mechanism of toxicity differs between lixivaptan and tolvaptan