**ABSTRACT**

**Objectives:** Lixivaptan, a vasopressin-2 receptor antagonist, is in development for the treatment of ADPKD, an orphan disease with high unmet medical need. The main objective of this research was to prospectively compare the potential for diuretic adverse drug reaction (ADR) to cause liver toxicity in a comparator drug in the same class, euvaptan, which has produced off-target liver signals in clinical trials.

**Methods:** In vitro data relating to reactive oxygen species formation, mitochondrial dysfunction, and bile acid transporter inhibition for lixivaptan and its metabolites were collected. Using these data, lixivaptan and its metabolites were represented in DILysim, a platform QST model of drug-induced liver injury. Lixivaptan PBPK was also represented in DILysim. Interpreting clinical trial PK data. Proposed ADPKD treatment dosing regimens were simulated and the predicted potential for liver enzyme elevations was compared to that previously determined for tolvaptan in DILysim.

**Results:** Lixivaptan was not predicted to cause liver enzyme elevations in a simulated human population which includes variability in toxicity susceptibility and pharmacokinetics, while tolvaptan was correctly predicted to cause rare liver enzyme elevations in a similar population (Table 1). Simulations at supratherapeutic doses suggest that potential liver toxicity mechanisms for lixivaptan are different from those identified for tolvaptan.

**Conclusions:** Lixivaptan was predicted to be safer than tolvaptan with respect to the liver toxicity mechanisms represented in DILysim. Quantitative and qualitative differences were identified between the two drugs. These findings pave the way for confirmatory clinical trials with lixivaptan in ADPKD.

**RESULTS**

**In Vitro Results**

**Calculated Parameter Comparison**

**METHODS**

**In vitro experiments** measured mitochondrial dysfunction, ROS generation, and bile acid transporter inhibition due to all four of the experimentalists in the mitochondrial assay and the ROS assay, a parallel culture was run to assess the intracellular concentration present in each assay; the assay results were corrected for these concentrations before the parameter values were calculated.

**PBPK Representation and Custom SimPops**

The PBPK representation for lixivaptan and its major metabolites was constructed using clinical data for optimization and validation. The clinical trials that were Phase I trial results (n=67) for seven-day 100 mg BID and 400 mg BID dosing regimens. The simulation results were compared to the data. Liver accumulation data from a rat WBAR study and from in vitro studies collected for this work was consistent with simulated liver concentrations.

**Simulation Results**

**Exposure-Toxicity Relationship**

The simulation of lixivaptan at the supratherapeutic dose of 400 mg BID shows a distinct relationship between exposure and ALTs. From this relationship, it is apparent that the expected exposure range for the 200 mg daily dose proposed for use in the clinic is well below which produces clinically significant (≥3X ULN) ALT elevations in the simulations. This also stands in contrast with tolvaptan, where no exposure-response relationship was found in the clinical trial. Simulations predicted lixivaptan to be less toxic than tolvaptan; while tolvaptan had significant ALT elevations in its SimPops simulation, lixivaptan had only sub-clinical ALT elevations. Simulations for lixivaptan suggested a low rate of ALT elevations at 400 mg BID, which suggests that the simulation results may be slightly conservative. ROS was found to be the main mechanism responsible for simulated ALT elevations at the supratherapeutic dose, in contrast with the case of tolvaptan in which bile acid accumulation and ETC inhibition were found to be the mechanisms of toxicity.

**CONCLUSION**

Simulations predicted lixivaptan to be less likely than tolvaptan to cause liver injury in clinical trials for ADPKD. Furthermore, the mechanistic differences between lixivaptan and tolvaptan were identified, suggesting that it would be even more unlikely for lixivaptan to replicate tolvaptan’s negative clinical experience. The simulations therefore support the continued development of lixivaptan for ADPKD treatment. This research demonstrates the potential for using QST techniques to prospectively compare mechanisms of the same class for toxic potential in order to select the molecule that is most likely to succeed.

**ACKNOWLEDGEMENTS**

• Palladio Biosciences, Inc.
• The members of the DILysim initiative

**REFERENCES**

Available upon request

**Correspondence:** l.j.woodhead@palladiobiosciences.com

**Prospective Liver Safety Comparison of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease (ADPKD) Using Quantitative Systems Toxicology Modeling**

Woodhead, J.L.*; Pellegrini, L.*; Siler, S.Q.*; Shoda, L.K.M.*; Watkins, P.B.*; Howell, B.A.*

*DILysim Services, Inc., a Simulations Plus Company, Research Triangle Park, NC, USA; *Palladio Biosciences, Inc., Newtown, PA