Prediction of the Liver Safety Profile of a First-in-Class Myeloperoxidase Inhibitor Using Quantitative Systems Toxicology Modeling

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PURPOSE

The novel myeloperoxidase inhibitor verdiperstat was developed as a treatment for neuroinflammatory and neurodegenerative diseases. Phase 2 clinical studies had shown some promise for efficacy at the 600 mg BID dose; however, this is a large dose and verdiperstat had shown some *in vitro* signals suggesting possible liver toxicity. Mild liver signals had also been observed during Phase 1 trials, though it was unclear whether these were drug-related or not. In order to provide an added layer of confidence in the liver safety of verdiperstat before proceeding to Phase 3, a computational prediction of verdiperstat liver safety was performed using DILIsym v8A, a quantitative systems toxicology (QST) model of liver safety.

METHODS

A physiologically-based pharmacokinetic (PBPK) model of verdiperstat was constructed in GastroPlus 9.8, and the estimates for the liver and plasma time course of verdiperstat were input into DILIsym. *In vitro* experiments measured the likelihood that verdiperstat would inhibit mitochondrial function, inhibit bile acid transporters, and generate reactive oxygen species (ROS). Predictions of liver verdiperstat exposure from the PBPK model and parameters derived from the *in vitro* experimental results were used as inputs into DILIsym. Two alternate sets of parameters were used as inputs in order to fully explore the sensitivity of model predictions within the potential range of the *in vitro* data. Verdiperstat dosing protocols up to 600 mg BID were simulated for up to 48 weeks using a simulated population (SimPops) in DILIsym.

RESULTS

In vitro experiments were conducted in cell vesicles (for bile acid transport) and HepG2 cells (for ROS and ETC inhibition). These experiments showed verdiperstat to be a mild inhibitor of the bile acid transporter MRP4 (Figure 1), a mild generator of ROS (Figure 2), and a mild inhibitor of the mitochondrial electron transport chain (ETC, Figure 3). For ROS and ETC inhibition, the intracellular concentration was measured by mass spectrometry.

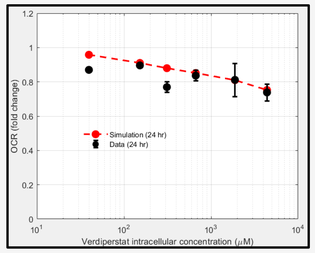


Figure 2. Relationship between measured intracellular verdiperstat and oxygen consumption rate, demonstrating a dose-dependent decrease in oxygen consumption and thus an inhibition of the electron transport chain.

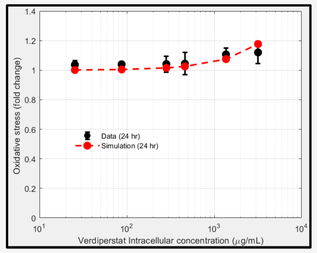


Figure 3. Relationship between measured intracellular verdiperstat and normalized TBARS generation, demonstrating a dose-dependent increase in oxidative stress.

Results from the *in vitro* experiments were used to calculate input parameters into DILIsym v8A, in the table below. OCR consumption was modeled in MITOsym v3B, a QST model of *in vitro* mitochondria, and translated into DILIsym; ROS generation was modeled in an *in vitro*-like parameterization in DILIsym (red lines in Figures 2 and 3). An alternate, conservative parameterization using an estimate of intracellular concentration as equal to the nominal concentration, which was suggested by the liver partition coefficient of 1 used in the PBPK model, was also developed; these parameters are also in the table below.

Mechanism	DILIsym Parameter	Unit	Alternate Verdiperstat Value	Primary Verdiperstat Value
BA Transport Inhibition	Inhibition constant for BSEP	μM	No inhibition	No inhibition
	Inhibition constant for basolateral efflux (MRP3/4)	μM	32.55**	32.55**
	Inhibition constant for NTCP	μM	No Inhibition	No Inhibition
Oxidative Stress	Liver RNS/ROS production rate constant 1	mL/nmol/hour	1.7×10^{-4}	1.15×10^{-6}
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	μM	6.94×10^{5}	6.94×10^{5}
	Coefficient for ETC Inhibition 3	μM	2.43	243
	Max inhibitory effect for ETC inhibition 3	Dimensionless	0.39	0.39

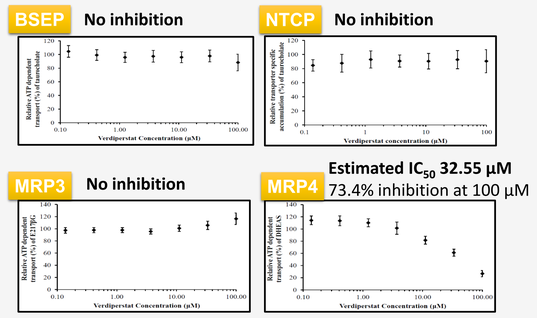
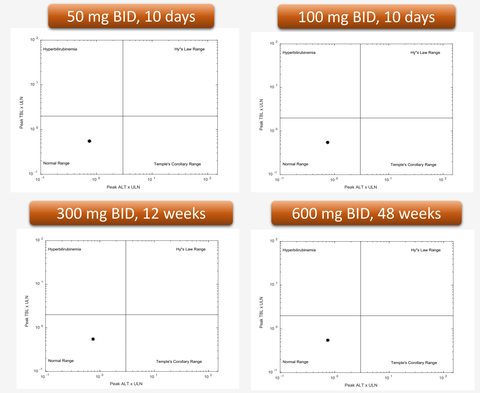
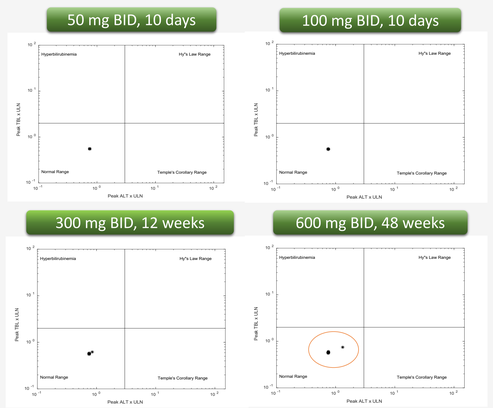


Figure 1. Inhibition of bile acid transporters by verdiperstat



In SimPops simulations (n = 285), no ALT elevations over 3x ULN were predicted using either the primary (above) or alternate (below) parameterizations. Mild ALT elevations (less than 3x ULN) occurred at the 600 mg BID dose in the alternate parameterization.



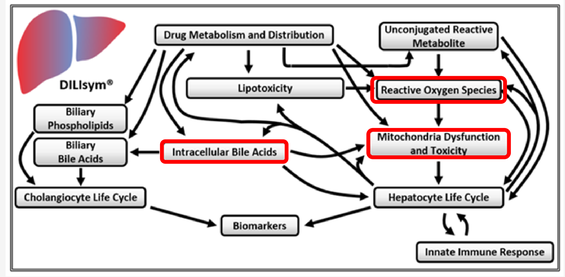


Diagram of the interactions between submodels in DILIsym v8A. In vitro *measurements of oxidative stress, mitochondrial dysfunction, and bile acid transport inhibition are used as inputs, and the DILIsym model of liver physiology computes the likelihood that those mechanisms will affect the hepatocyte life cycle, which will in turn affect biomarker release and immune system activation.*

CONCLUSION

Verdiperstat was predicted to be safe, with only rare, mild liver enzyme increases as a potential possibility in very highly sensitive individuals. Subsequent Phase 3 clinical trials conducted after the conclusion of this modeling work found that ALT elevations in the verdiperstat treatment group were generally similar to those in the placebo group. This validates the DILIsym simulation results and demonstrates the power of QST modeling to predict the liver safety profile of novel therapeutics.

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