Providing Insight into Novel Dosing Protocols Using a Quantitative Systems Pharmacology (QSP) Model of Drug-Induced Liver Injury

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ABSTRACT

Objective: Elevations in serum alanine aminotransferase (ALT) were observed in phase I clinical studies for a novel inpatient anti-infective therapy (Compound X). Previously conducted in vitro and cellular assays identified oxidative stress and mitochondrial electron transport chain (ETC) inhibition as potential mechanisms for the ALT elevations. A novel dosing protocol for Compound X had been proposed; this work would use quantitative systems pharmacology (QSP) modeling to predict the safety of this protocol.

Methods: A model for Compound X was created within DILIsym®, a QSP platform for predicting drug-induced liver injury (DILI). DILIsym® was then used to predict the potential safety margin for the novel Compound X dosing protocol.

Results: DILIsym® recapitulated the clinical dose response with reasonable accuracy after optimization. While the novel protocol had a narrow safety margin, DILIsym® results suggested that severe liver injury could be prevented if patients were monitored for ALT elevations daily and dosing halted when ALT was found to be above 3-fold higher than the upper limit of normal. Furthermore, the predicted safety margin of the drug improved when dosing was given on a weight-adjusted basis for each patient.

Conclusions: Modeling using DILIsym® suggested modifications to the dosing protocol that could potentially make the drug safer. These results suggest the utility of QSP methods in optimizing drug dosing protocols for maximum safety.

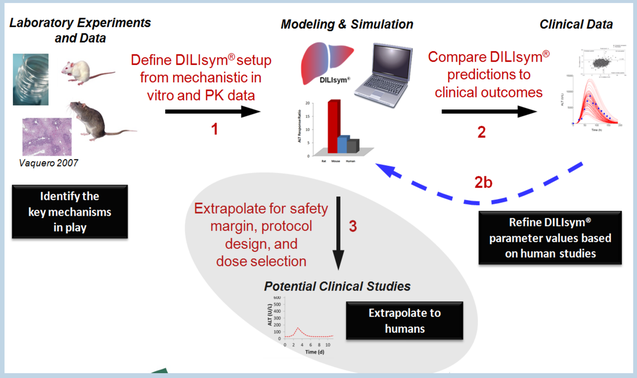
INTRODUCTION

- Compound X is a novel pharmaceutical developed for the treatment of an important short-term condition. It is designed to be dosed intravenously (IV) in an inpatient setting.
- Liver signals were observed in the clinic when 4x the proposed clinical dose was given daily as a 22-hour infusion and when a 2x dose was given thrice-daily as a 1-hour infusion.
- The company developing Compound X wished to explore a 4-hour IV infusion protocol using a 0.75x dose.
- DILIsym® was employed to explore the difference in toxicity among the existing protocols and to estimate the potential safety margin for the novel dosing protocol.

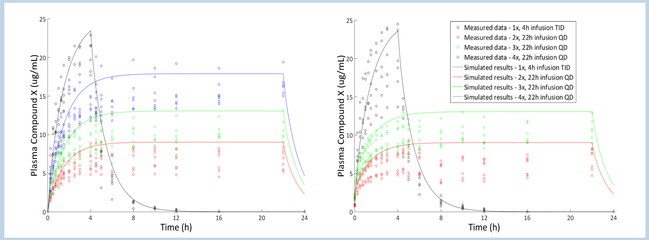
DILI-sim Initiative

RESULTS

Basic Workflow



PBPK Model



Above: Selected results for the PBPK model of Compound X on Day 1 (left) and Day 8 (right) of Compound X dosing.

Left: Workflow of the project, including the use of existing clinical data to further refine the toxicity model derived from extrapolation from *in vitro* assays.

Results for Existing Clinical Dosing Protocols

	1x t.i.d.				2x t.i.d.			
Simulated Exposure Level	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases
Low	0/300	181/300	0.94	0/300	216/300	300/300	0.94	0/300
Medium	23/300	296/300	0.96	0/300	299/300	300/300	0.78	1/300
High	119/300	300/300	0.95	0/300	300/300	300/300	0.39	2/300
Clinical data	1/7 ALT > 2x ULN (cK18 not measured)				2/6 ALT > 3x ULN 5/6 > 2x ULN (cK18 not measured)			

	2x (22 hour qd)				1x (4 hour tid)				3x (22 hour qd)				4x (22 hour qd)			
Simulated Exposure Level	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases
Low	0/300	2/300	0.98	0/300	0/300	128/300	0.95	0/300	0/300	130/300	0.94	0/300	5/300	278/300	0.92	0/300
Medium	0/300	67/300	0.96	0/300	4/300	269/300	0.93	0/300	1/300	243/300	0.94	0/300	45/300	299/300	0.96	0/300
High	0/300	187/300	0.93	0/300	26/300	298/300	0.95	0/300	12/300	293/300	0.91	0/300	110/300	300/300	0.93	0/300
Clinical data	Clean (cK18 not measured)				Clean (cK18 not measured)				Clean (cK18 not measured)				4/7 ALT > 3x ULN 4/7 elevated cK18			

Results for Novel Dosing Protocol

Results with Stop Protocol

	Low Exposure Level				Median Exposure Level				High Exposure Level			
Dose	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases
0.75x	0/300	58/300	0.96	0/300	0/300	189/300	0.93	0/300	4/300	274/300	0.91	0/300
1x	0/300	152/300	0.94	0/300	5/300	275/300	0.92	0/300	34/300	298/300	0.91	0/300
2x	49/300	300/300	0.90	0/300	186/300	300/300	0.90	0/300	274/300	300/300	0.89	0/300
3x	**201/300**	**300/300**	**0.90**	**0/300**	**296/300**	**300/300**	**0.83**	**0/300**	**300/300**	**300/300**	**0.16**	**29/300**
4.5x	299/300	300/300	0.81	0/300	300/300	300/300	0.15	59/300 (2)	300/300	300/300	0.15	145/300 (12)

Results without Stop Protocol

	Low Exposure Level				Median Exposure Level				High Exposure Level			
Dose	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases
0.75x	0/300	58/300	0.96	0/300	0/300	189/300	0.93	0/300	4/300	274/300	0.87	0/300
1x	0/300	152/300	0.94	0/300	5/300	275/300	0.87	0/300	34/300	298/300	0.76	0/300
2x	**49/300**	**300/300**	**0.73**	**1/300**	**186/300**	**300/300**	**0.15**	**36/300 (8)**	**274/300**	**300/300**	**0.15**	**127/300 (59)**
3x	201/300	300/300	0.15	47/300 (12)	296/300	300/300	0.15	202/300 (102)	300/300	300/300	0.15	288/300 (233)
4.5x	299/300	300/300	0.15	216/300 (113)	300/300	300/300	0.15	299/300 (277)	300/300	300/300	0.15	300/300 (300)

Results with Weight-Adjusted Dosing

	Low Exposure Level				Median Exposure Level				High Exposure Level			
Dose	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases	ALT	cK18	Min Viable Liver Fraction	Hy's Law Cases
0.75x	0/300	29/300	0.97	0/300	0/300	195/300	0.95	0/300	0/300	293/300	0.92	0/300
1x	0/300	148/300	0.96	0/300	0/300	293/300	0.91	0/300	16/300	300/300	0.91	0/300
2x	21/300	300/300	0.91	0/300	187/300	300/300	0.90	0/300	294/300	300/300	0.90	0/300
3x	213/300	300/300	0.90	0/300	300/300	300/300	0.91	0/300	300/300	300/300	0.83	0/300
4.5x	**300/300**	**300/300**	**0.91**	**0/300**	**300/300**	**300/300**	**0.72**	**13/300 (0)**	**300/300**	**300/300**	**0.15**	**205/300 (8)**

Legend

Simulation Color Key	
No elevations	
1-25% elevations	
26%-50% elevations	
51%-100% elevations	

Elevation definition		
	Clinical	Simulation
ALT	3x > ULN	> 90 U/L
cK18	2x > ULN	> 210 U/L

METHODS

- A PBPK model of Compound X was constructed using the PBPK sub-model in DILIsym® in order to predict potential liver exposure of the compound. Maximum and minimum exposure was represented by modulating the simulated dose.
- *In vitro* data on bile acid transporter inhibition, mitochondrial toxicity, and oxidative stress was generated. Compound X was shown to generate oxidative stress and to inhibit the mitochondrial electron transport chain (ETC). Compound X also mildly inhibited glycolysis.
- Toxicity parameter inputs calculated from the *in vitro* data were used to make initial predictions on toxicity in DILIsym®. Simulations in DILIsym® SimPops™ Human_ROS_apop_mito_v3B_1 were performed for each dosing regimen.
- Toxicity parameters were then adjusted so that the clinically observed dose response was recapitulated by DILIsym® while preserving the effect of the mechanisms flagged by the *in vitro* assays.
- Prospective predictions were made using these adjusted toxicity parameters for the proposed dose, escalating upwards until simulated toxicity was observed.
- The simulations were performed with and without strict ALT monitoring criteria and with weight-adjusted dosing in order to understand whether these protocol modifications improved the safety profile of Compound X.

CONCLUSION

- The margin of safety for the proposed 0.75x 4-hour infusion protocol was predicted to be small.
- Employment of a stringent stop protocol, where ALT is measured daily and dosing is stopped if an ALT elevation above 3X greater than the upper limit of normal (ULN) is observed, would increase the safety margin for severe liver injury.
- The safety profile of Compound X can be improved to 4.5x by dosing on a weight-adjusted basis.
- QSP modeling can be used to explore the toxicity risk of novel dosing protocols, allowing for the more informed selection of future clinical trials.

ACKNOWLEDGEMENTS

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- Company Y

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USING MECHANISTIC MODELING TO SOLVE LIVER TOXICITY PROBLEMS