Providing Insight into Novel Dosing Protocols Using a QSP Model of Drug-Induced Liver Injury

Jeffrey L. Woodhead, Scott Q. Siler, Brett A. Howell

DILIsym Services, Inc., RTP, NC, USA

Objective: Elevations in serum 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 (Table 1). 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.

Table 1. Recapitulation of clinical trial dose response of Compound X in DILIsym®.