Mechanistic modeling of drug-induced liver injury due to mtDNA depletion in DILIsym®

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Objective: To simulate drug-induced liver injury (DILI) due to mitochondrial DNA (mtDNA) depletion in DILIsym® using Fialuridine (FIAU) as an exemplar compound.

Methods: FIAU-induced mtDNA depletion and the subsequent effects on mitochondria function, hepatocellular bioenergetics, and liver injury were modeled in DILIsym® by combining predictions of compound exposure with compound-induced reductions in mtDNA synthesis. A simplified physiologically-based pharmacokinetic (PBPK) model was employed to simulate FIAU exposure. All PBPK parameters were calculated based on physio-chemical properties of FIAU or optimized to clinical PK data [1]. FIAU effects on hepatocyte function within DILIsym® were based on reductions in mtDNA synthesis and subsequent disruptions in mitochondrial function. Parameters describing the rate of FIAU-imposed mtDNA reductions were calculated based on in vitro data [2] and subsequently optimized based on clinical DILI responses [3]. The FIAU dosing protocol described by McKenzie et al. [3] was simulated with a SimCohort™, a group of simulated patients with variability in certain system-level parameters.

Results: DILIsym® accurately captures the plasma FIAU PK in humans (Figure 1A). DILIsym® also recapitulates the hepatotoxicity reported for extended treatment with FIAU [3]. A comparable frequency of severe liver injury was predicted in the SimCohort™ (11 out of 15 patients) as was reported for clinical patients (7 out of 10 patients). Delayed presentation of severe liver injury (>9 weeks) was also predicted in the simulated patients. The proportion of simulated patients with maximum total plasma bilirubin concentrations exceeding 3 mg/dL was comparable with the clinical patients (Figure 1B).

Conclusions: DILIsym® accurately simulates DILI due to FIAU administration and can be used to evaluate the DILI risk of compounds that have the potential to deplete mtDNA. Further investigation will be required to translate in vitro data into DILIsym® input parameters for drug-imposed mtDNA reductions.

References: