Proof-of-concept Simulations Using BIOLOGXsym™, a Novel Quantitative Systems Toxicology (QST) Modeling Platform for Predicting Biologics-induced Liver Injury (BILI), Recapitulate Clinically Observed Hepatotoxicity of GGF2

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BACKGROUND

- While biologics continue to address various unmet medical needs, BILI can terminate clinical development of promising treatments such as cimaglermin alfa (GGF2)
- Elevations of BILI biomarkers (plasma ALT and TB) were observed in phase I clinical trials of GGF2
- To assess clinical BILI risk of biologics such as GGF2, a novel QST modeling platform, BIOLOGXsym™, was developed in conjunction with assay outputs from a biomimetic liver model

METHODS

- BIOLOGXsym™ software was engineered to mathematically represent relevant liver biochemistry and mechanistic effects of biologics on liver pathophysiology
- 10-day GGF2 (10 ng/mL) treatment of a human (vascularized) liver acinus microphysiology system [(v)LAMPS] provided GGF2-dependent readouts from previously validated assays
- Mechanistic data on GGF2 from (v)LAMPS and literature[1], and GGF2 exposure predictions using GastroPlus® (**Fig. 1**) were integrated to simulate GGF2 hepatotoxicity in BIOLOGXsym™

RESULTS

- Treatment of (v)LAMPS with GGF2 significantly decreased bile acid secretion (**Fig. 2**)
- These and other[1] GGF2 data were used to derive mechanistic toxicity parameters in BIOLOGXsym™
- Simulations furthermore incorporating population variability reasonably recapitulated the range of plasma ALT and TB observed in GGF2 clinical trials[2] (**Fig. 3**)

REFERENCES: [1]Mosedale *et al. Toxicol Sci.* 2018 Feb;161(2):401-411; [2]Longo *et al. Clin Pharmacol Ther*. 2017 Dec;102(6):961-969.

Novel mathematical and microphysiological models of the human liver show the potential to predict - **and provide mechanistic insights to explain** - clinically observed hepatotoxicity of biologics

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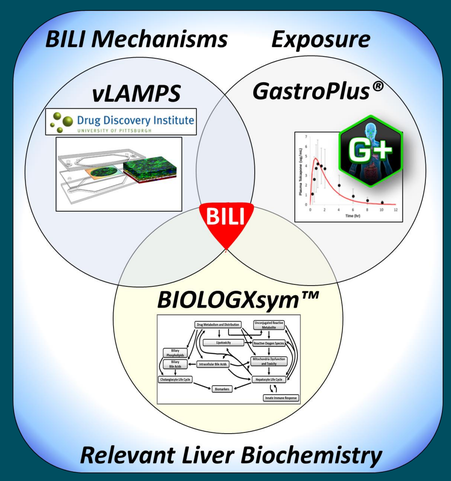

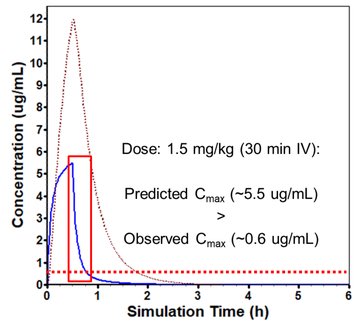

Figure 1. Clinical GGF2 exposure in plasma (solid blue curve) and the hepatic interstitium (dotted maroon curve) was simulated by physiologically based pharmacokinetic modeling using GastroPlus®. C_{max}, maximum plasma concentration; IV, intravenous administration

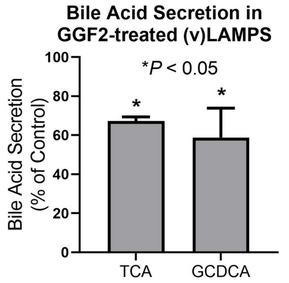

Figure 2. GGF2-dependent bile acid secretion in (v)LAMPS. Error bars represent SD. *, significantly different from vehicle-treated control; GCDCA, glycochenodeoxycholate; TCA, taurocholate

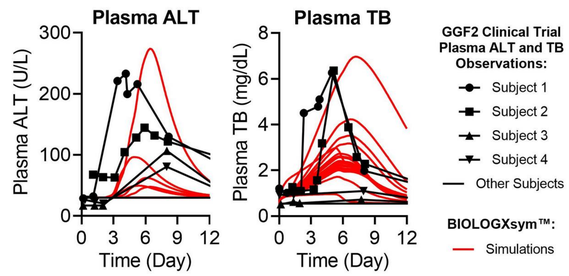

Figure 3. GGF2-dependent clinical observations and BIOLOGXsym™ simulations of plasma ALT and TB profiles. ALT, alanine aminotransferase; TB, total bilirubin

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose