# Predicted Liver Safety of GlyphAgo, a Lymphatic-targeting Prodrug of Agomelatine That Avoids First-pass Metabolism

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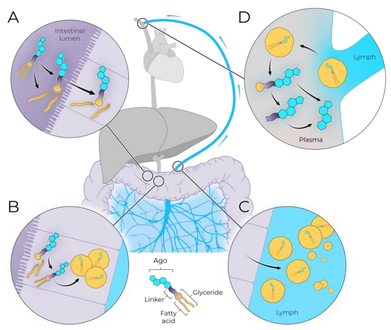
## Introduction

- Agomelatine, a melatonin 1 & 2 receptor agonist and serotonin 2C receptor antagonist, is an effective anxiolytic and antidepressant approved for treatment of generalized anxiety disorder (GAD; Australia) and major depressive disorder (Australia/EU)
  - Efficacy and tolerability of agomelatine in GAD is favorable to benzodiazepines and SSRIs[1]
- However, agomelatine undergoes extensive first-pass metabolism (over 90%), resulting in low bioavailability, variable exposure, and occasional dose-dependent elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST)[2,3]




- Therefore, routine liver monitoring is required in regions where it has received regulatory approval, a requirement cited as a significant barrier to clinical use[1]
- GlyphAgo™ (SPT-320 or Glyph Agomelatine) is an oral prodrug of agomelatine designed with the Glyph™ platform, a prodrug technology that shifts absorption toward intestinal lymphatics, avoiding first-pass metabolism
- GlyphAgo has the potential to avoid first-pass metabolism and increase systemic exposure at a lower dose that may reduce liver exposure and reduce/eliminate the need for liver function testing
- We report the results of DILIsym®, a quantitative systems toxicology model of drug-induced liver injury (DILI) to predict the reduction of liver enzyme elevation risk of simulated GlyphAgo dosing relative to agomelatine

## Methods

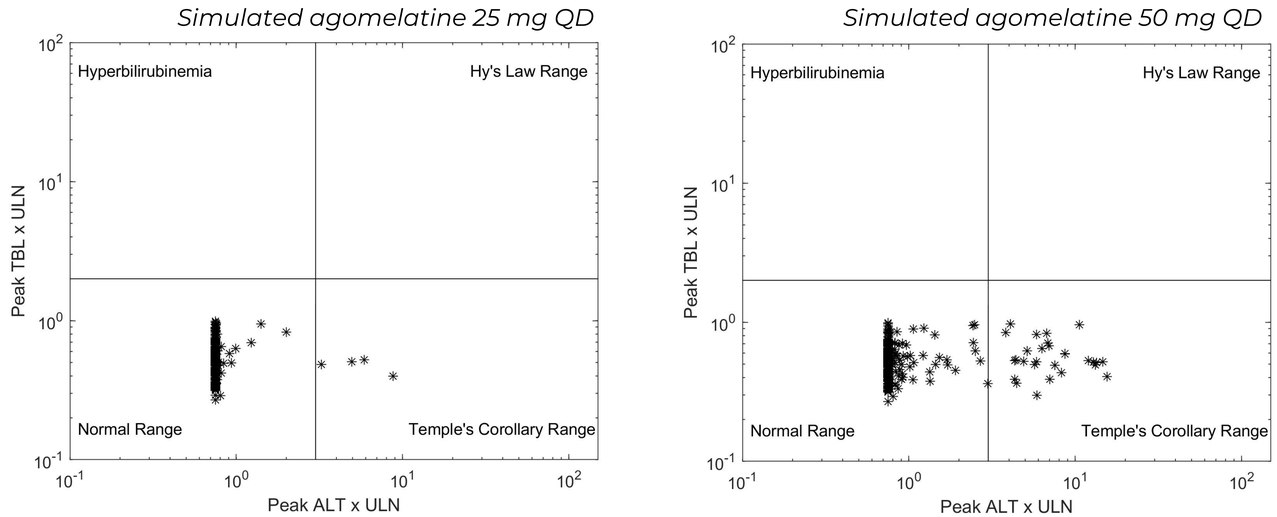
- DILIsym combines measures of modeled compound exposure at the site of action (i.e., liver) with concentration-dependent hepatocyte toxicity and inter-individual variability to predict liver injury
- A physiologically based pharmacokinetic (PBPK) model was developed to predict liver concentrations of simulated doses of agomelatine based on published preclinical and clinical data of agomelatine
- A CYP1A2-derived agomelatine metabolite, which may drive hepatotoxicity[4], was optimized to induce hepatocyte cell death, empirically reproducing dose-dependent ALT elevations ≤10% at approved doses of agomelatine in a simulated population (SimPops; N=285)
- The PBPK model was adapted to represent GlyphAgo, where bypassing first-pass metabolism via lymphatic absorption was represented by intravenous administration
- Infusion kinetics were designed to match the circulation profile of lymphatically-absorbed dietary fats and previously reported Glyph prodrugs[5]
- Dosing simulations to predict DILI were conducted in SimPops with approved 25 and 50 mg once daily (QD) dosing of agomelatine and GlyphAgo doses achieving comparable agomelatine plasma concentrations to oral agomelatine

## Discussion

- DILIsym modeling showed that simulated oral dosing of agomelatine caused liver enzyme elevations while doses of GlyphAgo achieving comparable agomelatine exposure did not
- By leveraging the Glyph platform to shift absorption to the intestinal lymphatics, GlyphAgo may be able to reduce or eliminate liver enzyme elevation risk by avoiding first-pass metabolism
- These results suggest that GlyphAgo may facilitate clinical applications of agomelatine without the need for routine liver monitoring
- This work supported an ongoing phase 1 proof-of-concept clinical trial of GlyphAgo in healthy volunteers evaluating the safety, tolerability, and pharmacokinetics compared to agomelatine which is currently underway

## Results

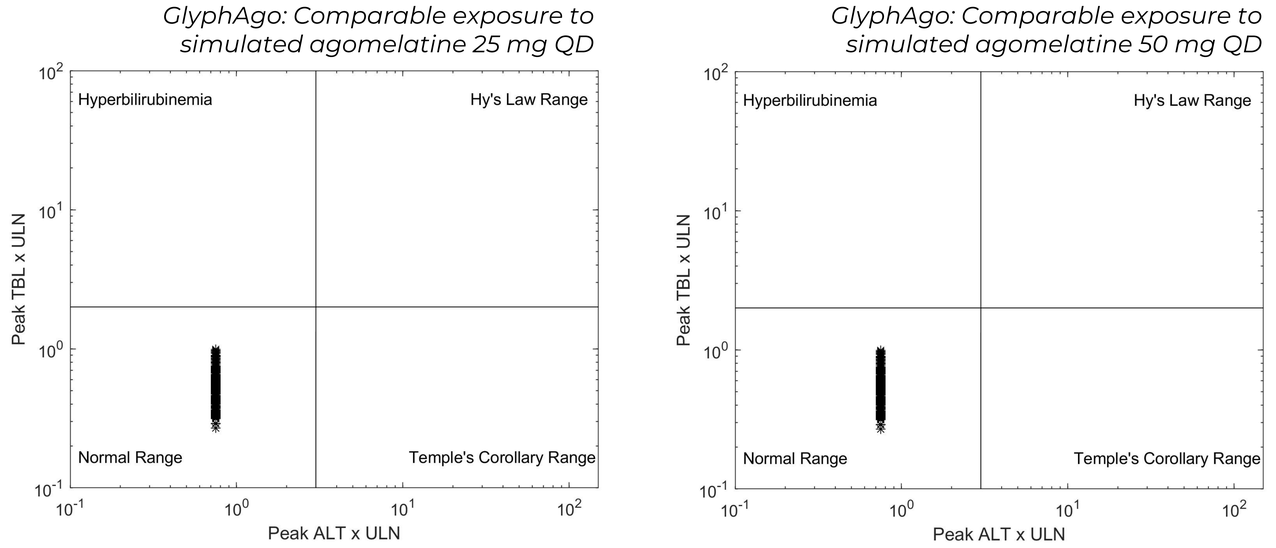
**Figure 1. DILIsym modeling recapitulates the liver enzyme elevations observed in previous clinical trials of agomelatine.**




Asterisks represent one simulated patient from SimPops

- Mean $C_{max}$ and AUC values generally fell within ~2x of reported values
- In DILIsym, cell death parameters were optimized to yield 1.4% and 9.5% ALT elevations in SimPops following simulated treatment with approved 25 or 50 mg QD AGM dosing, respectively
- While 9.5% is significantly higher than the observed 50 mg ALT elevation rate of 2.4% in clinical trials of agomelatine[1], this was applied to provide an additional safety factor for estimated GlyphAgo ALT elevation rates

**Figure 2. DILIsym modeling of GlyphAgo dosing yielded no liver enzyme elevations in SimPops.**




Asterisks represent one simulated patient from SimPops

- In simulations, GlyphAgo did not precipitate 3x ULN ALT increases until the dose was raised to produce exposures exceeding those of the simulated approved agomelatine dose, suggesting the potential to deliver active drug with minimal hepatic consequences

ALT, alanine aminotransferase; QD, once daily; TBL, total bilirubin; ULN, upper limit of normal

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**References:** 1. Slee A et al. 2019; Lancet, 393: 768-77. 2. Perlemuter G et al. 2016; CNS Drugs, 30(9): 877-888. 3. Committee for Human Medicinal Products (CHMP). Assessment Report for Valdoxan. November 2008. 4. Bogaards JJP et al. Eur J Pharm Sci. 2000 Dec;12(2):117–24. 5. Simpson J et al. Neuroscience Applied. 2026;5:106064.
**Disclosures:** DKB, ST, JSS, and MCC are employees of Seaport Therapeutics. RM is an employee of Apex Drug Discovery and Innovation Strategies, LLC and is a consultant for Seaport Therapeutics. LS is an employee of Simulations Plus.
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