Prediction of Human Pharmacokinetic Profiles of Glyph Platform Prodrugs Using Animal and Human Data via a Semi-mechanistic Pharmacokinetic Model

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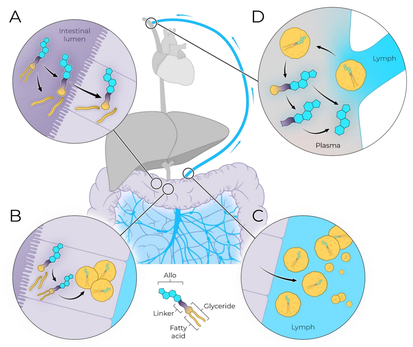
Introduction

- GlyphAllo™ (SPT-300 or Glyph™ Allopregnanolone) is an oral prodrug of allopregnanolone designed to avoid first-pass hepatic metabolism by shifting absorption toward intestinal lymphatics
- GlyphAllo uses the Glyph platform, a lymphatic-targeting prodrug technology which reversibly conjugates a drug of interest to a dietary fat molecule using linker chemistry
- This route of absorption enables higher oral bioavailability of allopregnanolone at lower doses, potentially reducing side effects
- Recently, a phase 1 clinical trial demonstrated that GlyphAllo was generally well tolerated and resulted in therapeutically relevant allopregnanolone plasma exposures in healthy volunteers[1]
- Here, we developed a semi-mechanistic pharmacokinetic (PK) model to predict human exposures for lymphatic-targeting Glyph prodrugs from preclinical data



Methods

- Allopregnanolone PK profiles were obtained after a single oral dose of GlyphAllo in cynomolgus monkeys and a first-in-human phase 1 study (NCT05129865)
- A semi-mechanistic PK model was developed with an absorption compartment, five transit compartments to account for the unique absorption kinetics of dietary lipids, and central and peripheral compartments to describe both the non-human primates (NHP) and human profiles (Figure 1)
- The methodology to predict human allopregnanolone profiles from nonhuman primates (NHP; Figure 2) consisted of the following:
  - Using reverse interspecies scaling, clearance (CL), central volume (V1), peripheral volume (V2), and inter-compartmental rate transfer (Q), NHP PK parameters were obtained from a published human intravenous allopregnanolone population PK model[2]
  - To capture the unique absorption kinetics of lymphatic delivery, optimal absorption (ka) and transit rate (k_{tr}) PK parameters were fit to the semi-mechanistic PK model using the NHP allopregnanolone concentration-time profiles
  - These parameters (ka, k_{tr}) derived from NHP were combined with published human parameters[1] to model profiles measured in the phase 1 study

Figure 1. Semi-mechanistic model describing GlyphAllo PK.

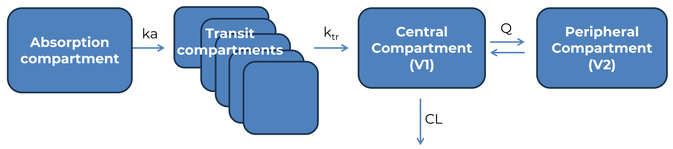
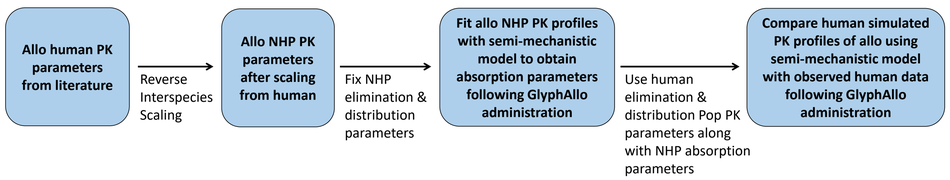


Figure 2. Methodology for predicting human allopregnanolone PK from NHP.



- All model building and graphical analyses were done using NLMIXR2 (Version 3.0.2), RStudio (Version 2024.12.0), and R (Version 4.4.2)

Results

- The visual predicted checks showed that the semi-mechanistic model was able to effectively capture the observed profiles in NHP (Figure 3)
- Similarly, human allopregnanolone profiles were well described by the semi-mechanistic PK model (Figure 4)

Figure 3. Visual predicted checks of observed and predicted 5th, 50th & 95th percentile allopregnanolone concentrations in NHP using semi-mechanistic PK model.

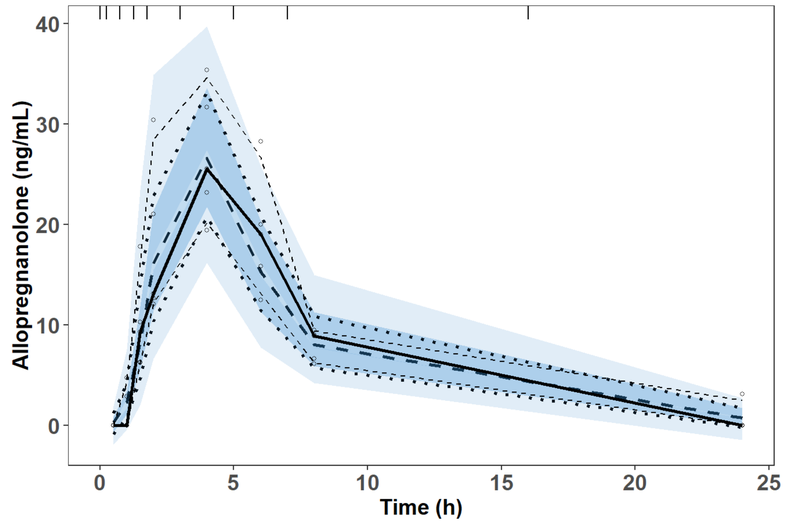
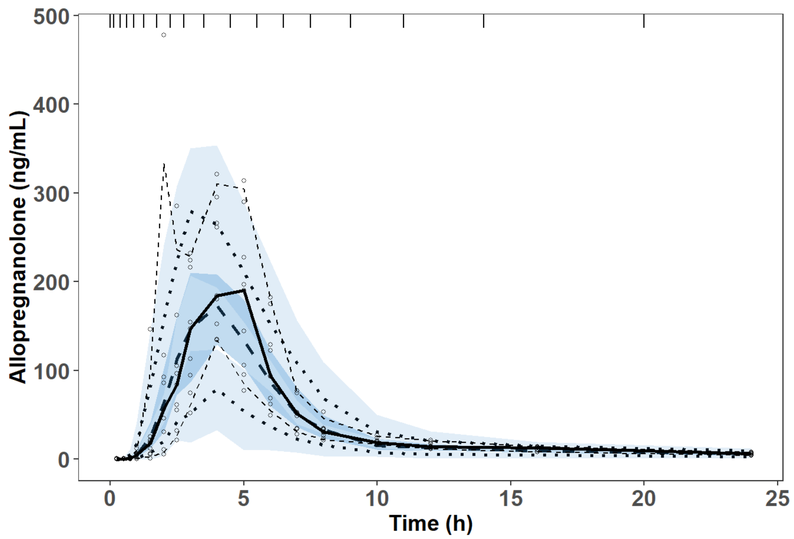


Figure 4. Visual predicted checks of observed and predicted 5th, 50th & 95th percentile allopregnanolone concentrations in humans using semi-mechanistic PK model.



CL, clearance; ka, optimal absorption; k_{tr}, transit rate; NHP, nonhuman primates; PK, pharmacokinetic; Q, compartmental rate transfer; V1, central volume; V2, peripheral volume.

Discussion

- We present a modeling approach to predict human exposures of lymphatic-targeting Glyph prodrugs by first using human PK data of existing drugs and back-transforming them to animal PK data, then subsequently fitting optimal absorption and transit compartment parameters in cynomolgus monkey to capture complex lymphatic absorption kinetics
- These absorption parameters from cynomolgus monkeys, along with published human kinetic parameters were then used for modeling human exposures of lymphatic-targeting Glyph prodrugs
- Results illustrate the interspecies scaling of GlyphAllo and support the application of this method to predict PK across species for other Glyph molecules in development
- BUOY-1 (NCT07065240), a phase 2b study of the efficacy, safety, tolerability, and PK of oral GlyphAllo as monotherapy in adults with MDD, with or without anxious distress, and its 6-week open-label extension (NCT07161700) are both currently underway

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References: 1. Simpson JS et al. Sci. Transl. Med. 2026;18(842). 2. Wald J et al. Clin Pharmacokinet. 2022;61:1307–1319.
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