

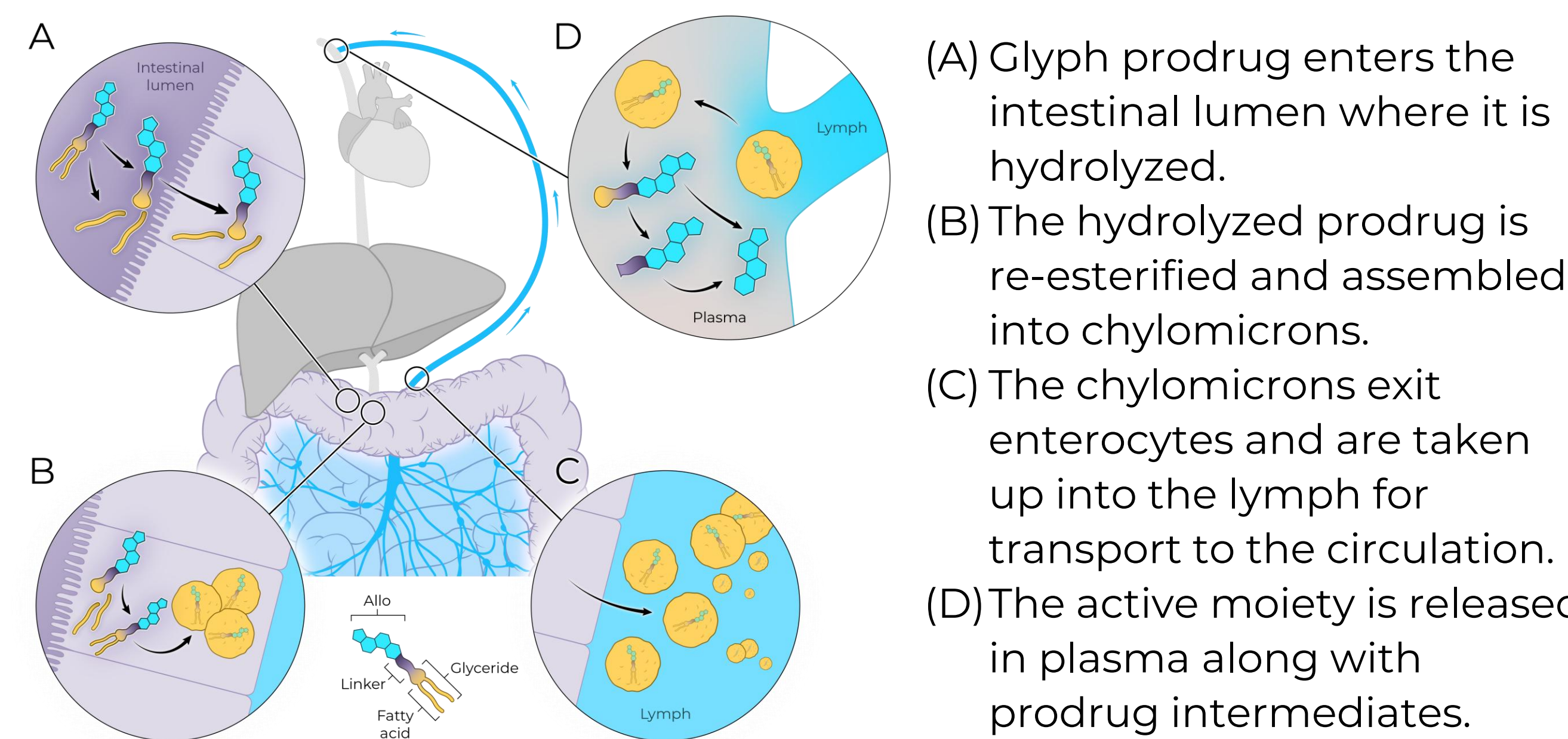
Population Pharmacokinetic Modeling of Oral GlyphAllo in Healthy Volunteers Strengthens Evidence for Lymphatic Absorption of Glyph Prodrugs



Kosalaram Goteti¹, Rena Eudy-Byrne², Jia Kang², Haiyuan Zhu¹, Daniel K. Bonner¹, Michael C. Chen¹
¹Seaport Therapeutics, Boston, MA; ²Metrum Research Group, Boston, MA

Introduction

- GlyphAllo™ (SPT-300 or Glyph Allopregnanolone) is an oral prodrug of allopregnanolone designed with the Glyph™ platform to overcome allopregnanolone’s poor oral bioavailability due to substantial first-pass hepatic metabolism¹
 - Allopregnanolone is an endogenous neurosteroid that has been clinically validated as an antidepressant with anxiolytic and sleep-promoting effects
- The Glyph™ platform, a lymphatic-targeting prodrug technology, reversibly conjugates a drug of interest to a dietary fat molecule to shift absorption toward the intestinal lymphatics to address limitations of high first-pass hepatic metabolism, low oral bioavailability, and/or side effects
- **Objective:** Here, initial clinical data collected across healthy volunteers were used to develop a population pharmacokinetic (PK) model to characterize the disposition of allopregnanolone following oral administration of GlyphAllo



Methods

- Data were pooled from healthy volunteers in clinical trials receiving oral GlyphAllo
- Subject demographics and characteristics, such as baseline body weight, sex, race, and fed or fasted condition, were considered for modeling
- Different absorption models were tested, including first-order absorption, sequential zero- and first-order absorption, and various transit compartment absorption models using NONMEM® version 7.5 (ICON PLC, Ireland), and data evaluation was conducted in R (version 4.5)
- Model performance was assessed by goodness-of-fit plots, model stability, precision around parameter estimates, and visual predictive checks

Results

- PK measurements of allopregnanolone were obtained from 166 healthy volunteers (5656 total PK measurements)
- 6.6% of all PK observations were below the limit of quantification
- The final model was a two-compartment disposition model with linear elimination and a transit-compartment absorption model (Figure 1)
 - The number of transit compartments was estimated using Stirling’s approximation²
 - Covariates of fasted condition on mean transit time (MTT) and F₁, body weight on CL/F and V/F were included in the final model

Figure 1: Semi-mechanistic model describing GlyphAllo PK.

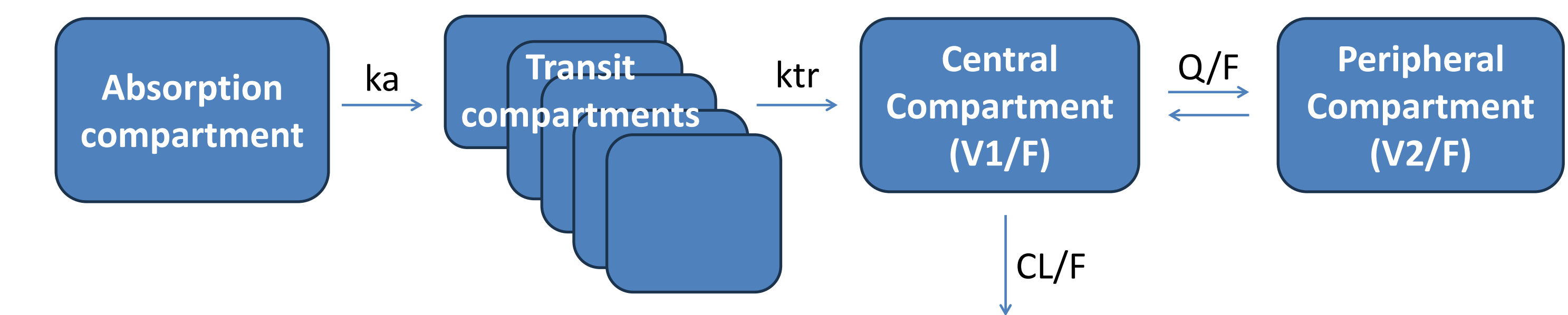
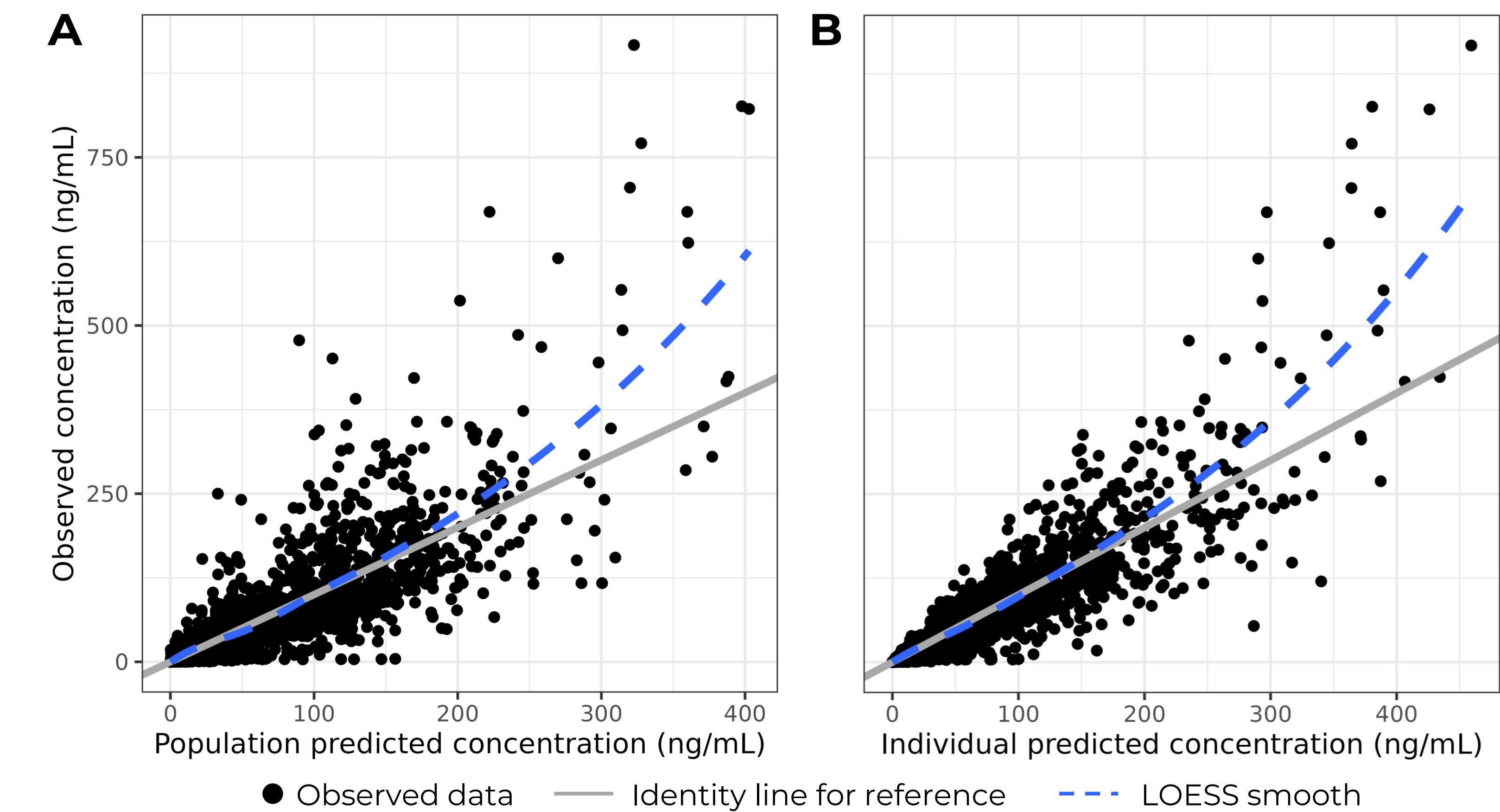
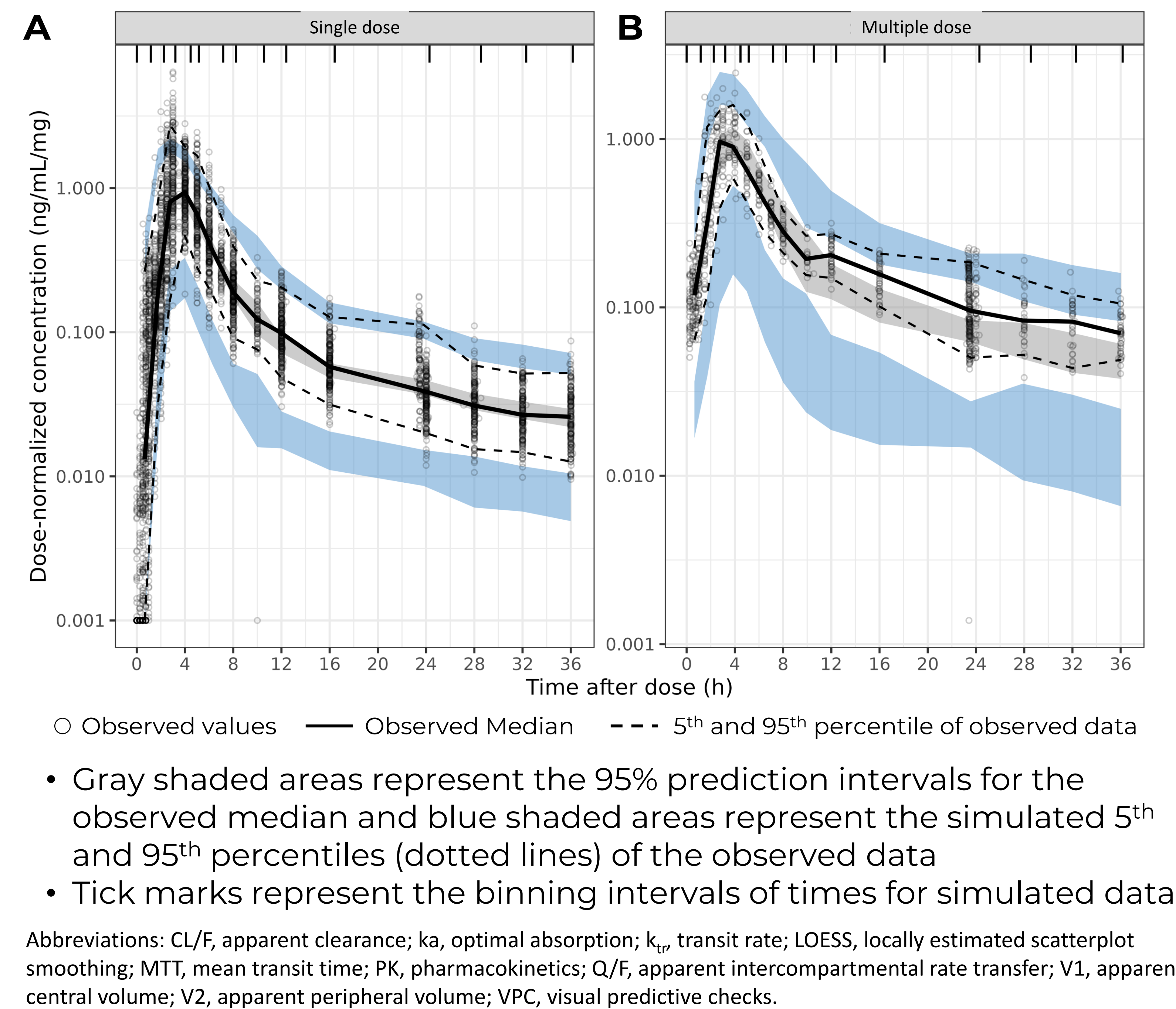


Figure 2: Observed allopregnanolone plasma concentration vs A) population and B) individual predicted concentrations based on final population PK model.



- Models with first-order absorption, sequential zero- and first-order absorption, and a fixed number of transit compartments did not result in a better fit to the data as determined by objective function value
- The final model provided a good fit to observed clinical trial data according to diagnostic plots for both the population and individual predictions (Figure 2)
- Visual predictive checks (VPCs) show that the final model provided a good fit to observed concentration-time profile after single ascending doses and multiple ascending doses of GlyphAllo (Figure 3)

Figure 3: Visual predictive checks of dose normalized allopregnanolone plasma concentration after A) single ascending doses and B) multiple ascending doses of GlyphAllo.



Conclusions

- A population PK model was developed that we estimate adequately described allopregnanolone pharmacokinetics following oral administration of GlyphAllo in healthy volunteers across the evaluated dose range
- The model provides a quantitative framework to predict GlyphAllo pharmacokinetics across treatment cohorts and results may support the application of the population pharmacokinetics model to future clinical trials of Glyph-enabled prodrugs

Funding sources: Research sponsored by Seaport Therapeutics. ClinicalTrials.gov Identifier: NCT05129865.
References: 1. Simpson et al. Sci. Transl. Med. 2026. 18(842). 2. Savic et al. J Pharmacokinet. Pharmacodyn. 2007. 34(5).
Disclosures: KG, HZ, DKB, and MCC are employees of Seaport Therapeutics. REB is an employee of Metrum Research Group. JK was an employee of Metrum Research Group at the time the analysis was conducted.

