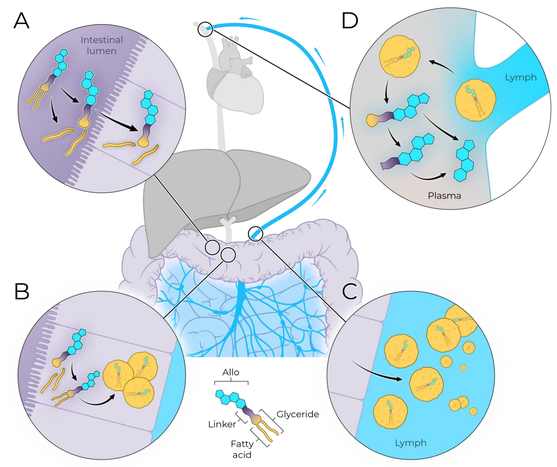
Population Pharmacokinetics of Oral GlyphAllo in Healthy Volunteers

Kosalaram Goteti[1], Rena Eudy-Byrne[2], Jia Kang[2], Haiyuan Zhu[1], Daniel K. Bonner[1], Michael C. Chen[1]
[1]Seaport Therapeutics, Boston, MA; [2]Metrum 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 metabolism[1]
  - 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



(A) Glyph prodrug enters the intestinal lumen where it is hydrolyzed.
(B) The hydrolyzed prodrug is re-esterified and assembled into chylomicrons.
(C) The chylomicrons exit enterocytes and are taken up into the lymph for transport to the circulation.
(D) The active moiety is released in plasma along with prodrug intermediates.

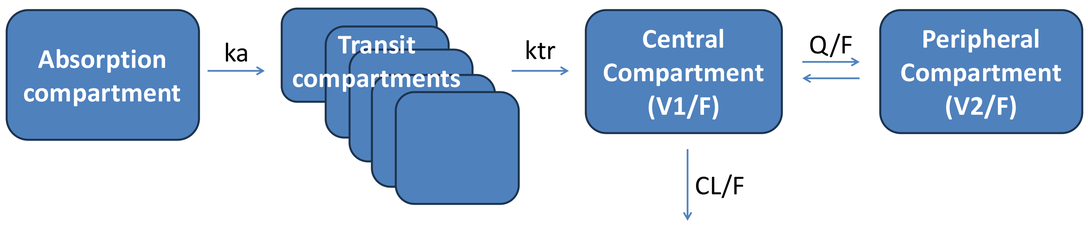
Methods

- Data were pooled from healthy volunteers receiving oral GlyphAllo or placebo
- 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
- Model performance was assessed by goodness-of-fit plots, model stability, precision around parameter estimates, and visual predictive checks
- Nonlinear mixed effect modeling analysis was performed using NONMEM® version 7.5 (ICON PLC, Ireland)
- Data manipulation, visualization, and simulations were conducted using R version 4.5

Results

- A total of 5656 PK measurements were obtained from 166 healthy volunteers
- 6.6% of all PK observations in GlyphAllo receiving volunteers 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 were estimated using Stirling's approximation[2]
  - 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.



CL/F, apparent clearance; ka, optimal absorption; k_{tr}, transit rate; Q/F, apparent intercompartmental rate transfer; V1, apparent central volume; V2, apparent peripheral volume.

- 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 data according to diagnostic plots for both the population and individual predictions (Figure 2)
- Visual predictive checks 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 2: Observed allopregnanolone concentration vs A) population and B) individual predicted concentrations based on final population PK model for various parts of the phase 1 clinical trial.

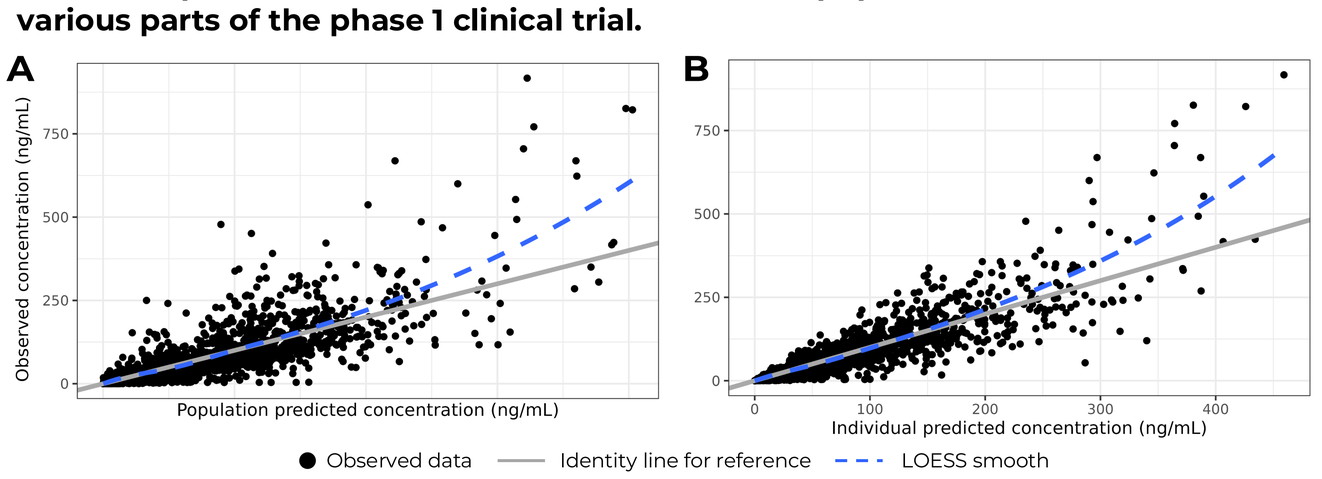
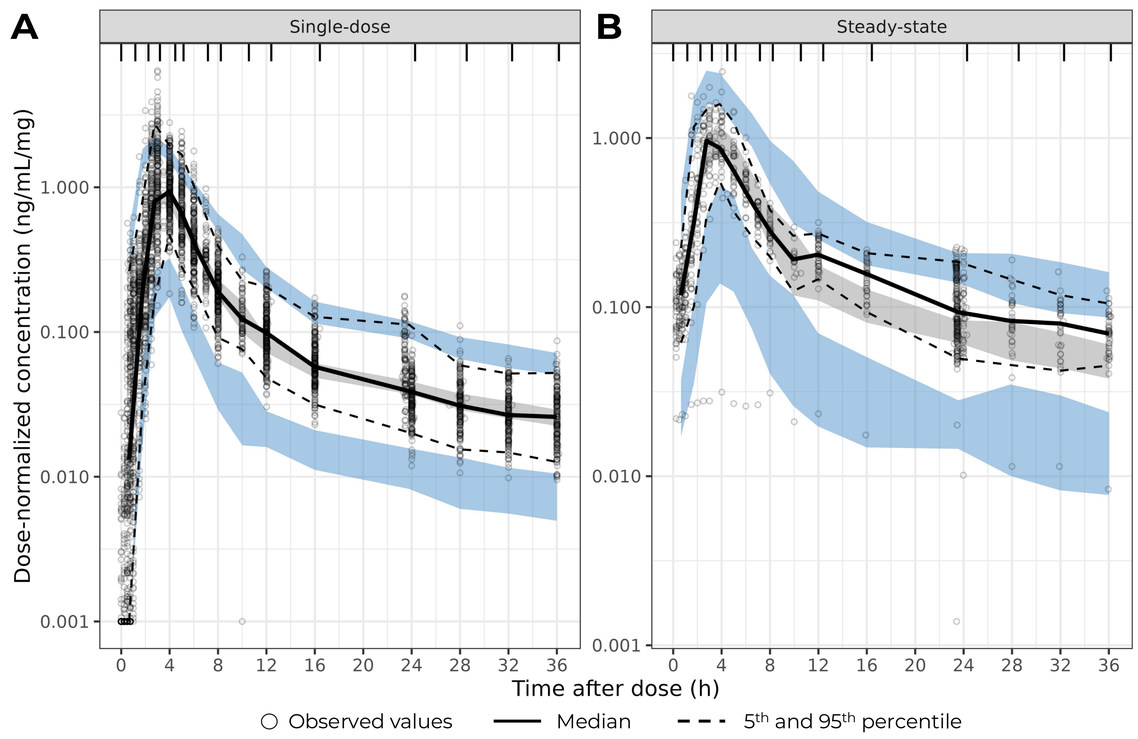


Figure 3: Visual predictive checks of dose normalized concentration of allopregnanolone after A) single ascending doses and B) multiple ascending doses in a phase 1 clinical trial.



Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue of the simulated data. Tick marks represent the binning intervals of times.

Conclusions

- A population PK model was developed that 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 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.
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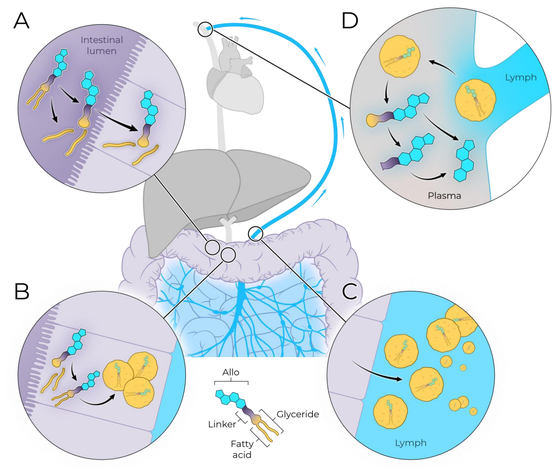

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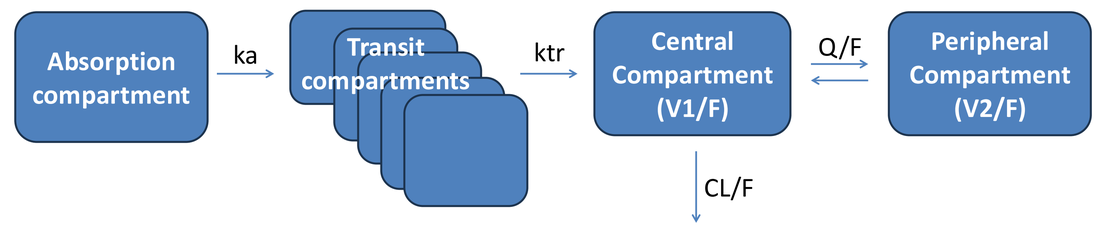

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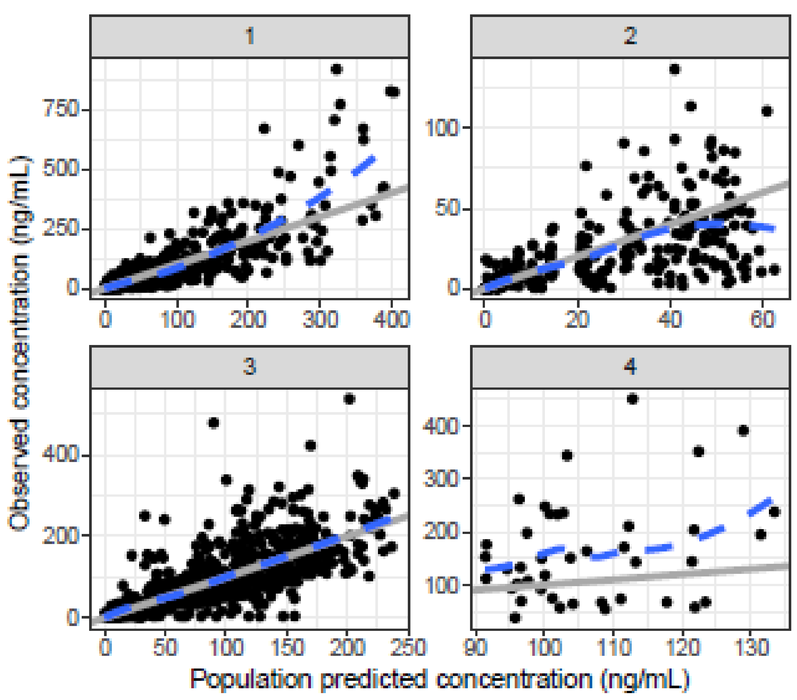
Figure 2: Observed vs Population Predicted concentrations based on Final Population PK model for various parts of the Phase 1.



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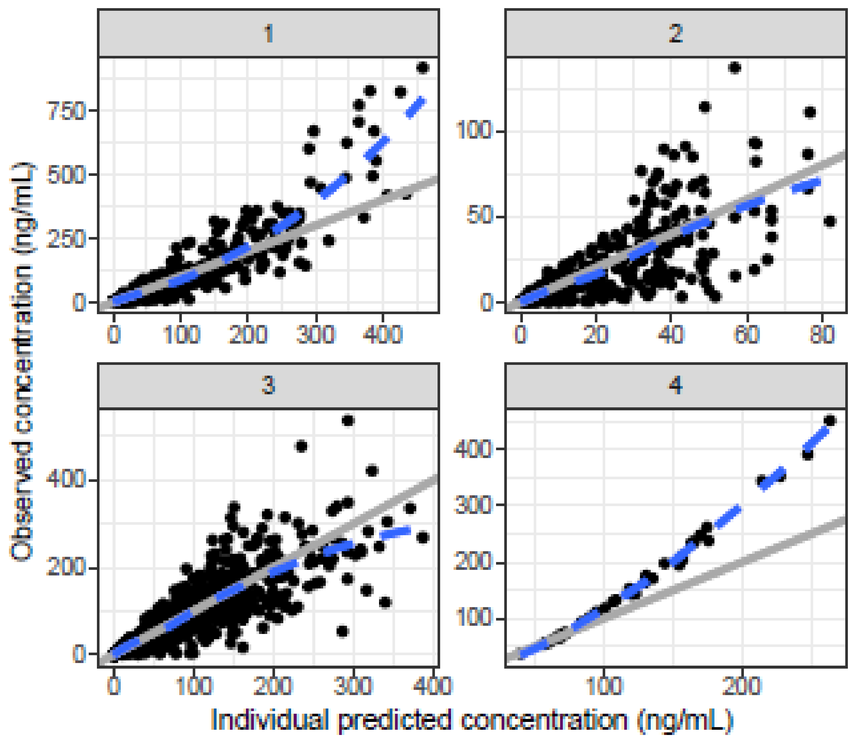

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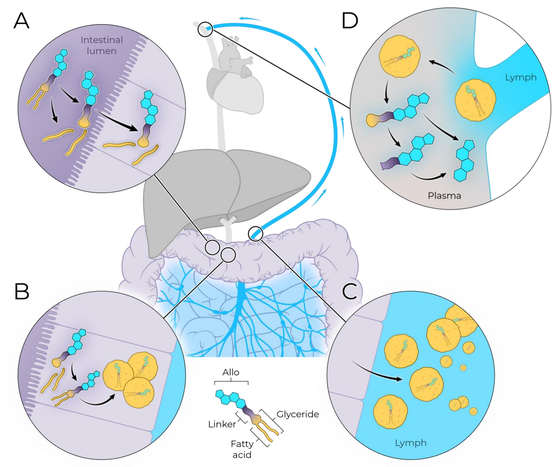

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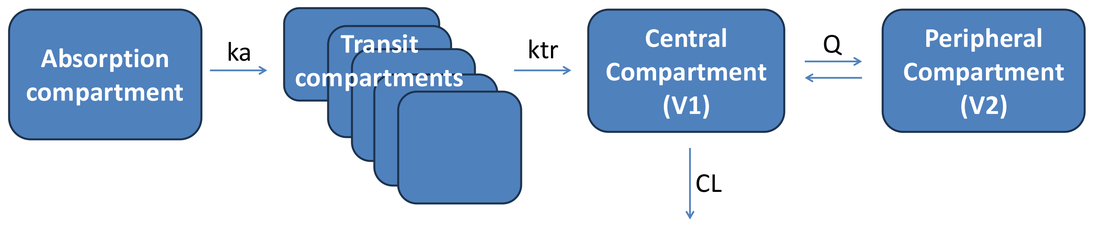

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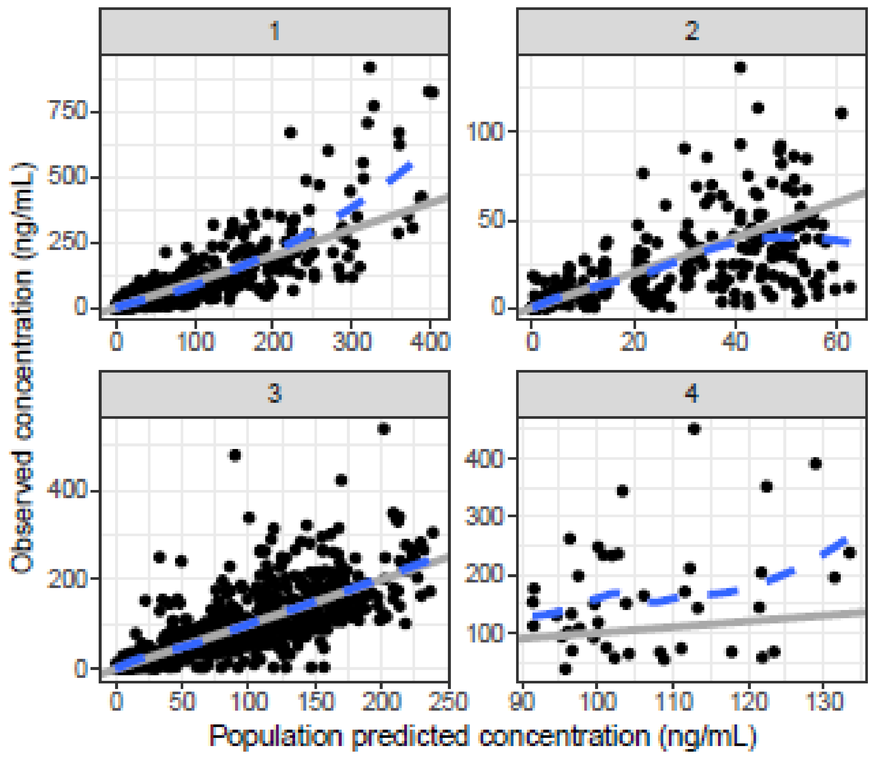

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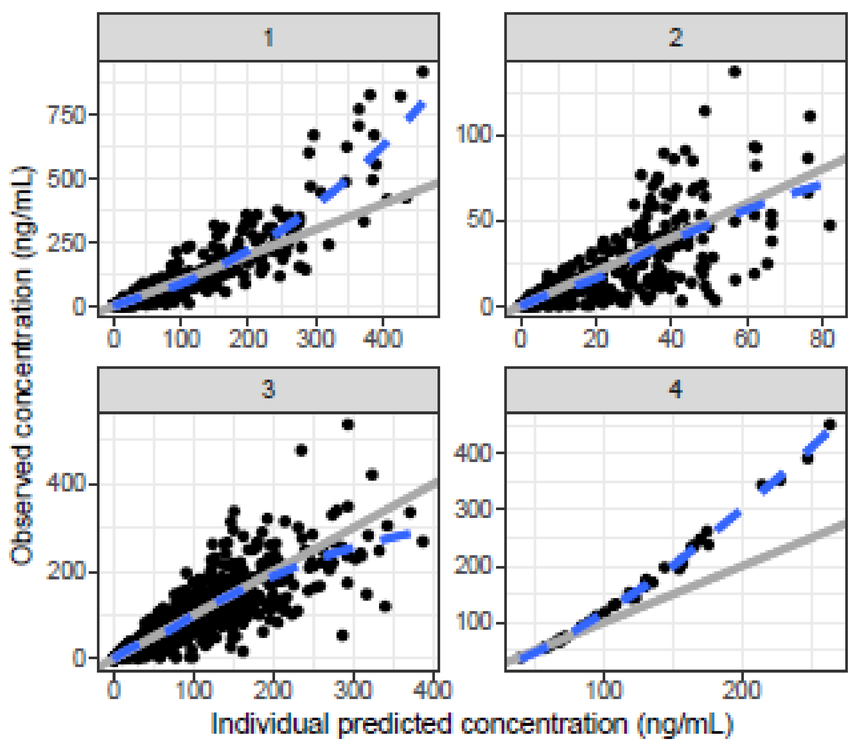

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