A Population Pharmacokinetic Model of Samidorphan Following Sublingual Administration of ALKS 5461 in Patients With Major Depressive Disorder

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Background

- ALKS 5461 (a fixed-dose sublingual (SL) combination of buprenorphine and samidorphan (SAM)) is currently under clinical development for the adjunctive treatment of major depressive disorder (MDD) in patients who have an inadequate response to standard therapies.[1]
- SAM is a novel opioid receptor antagonist with high affinity at the μ-opioid receptor. SAM was added to address the abuse and dependence potential associated with buprenorphine.

Aim

- The objectives of the analysis were to characterize the PK of SAM following SL administration of ALKS 5461, and to identify the covariates that can explain between-subject variability in the PK of SAM.

Methods

- Data from 10 studies (healthy volunteers, patients with MDD, renal and hepatic impairment) were included in the analysis.
- A non-linear mixed effects model was developed in NONMEM v7.3.
- Diagnostics, numerical, and prediction-corrected visual predictive checks were used to evaluate the model.
- Forest plots were constructed to evaluate the magnitude of covariate effects on SAM exposure.

Conclusions

- A population PK model for SAM following SL administration of ALKS 5461 was developed that adequately described the PK of SAM in healthy subjects and MDD patients.
- Age, weight, gender, race, or concomitant treatment of ADTs showed no effect on the PK of SAM in ALKS 5461.
- The increased SAM exposures from population PK analysis for subjects with hepatic impairment and severe renal impairment were comparable to the results observed from clinical studies, indicating good model predictability.
- Model-based simulations indicated that mild to moderate renal impairment had no clinical relevant influence on the PK of SAM in ALKS 5461.

References

1. Fava M. Am J Psychiatry. 2016 May 1;173(5):499-508.

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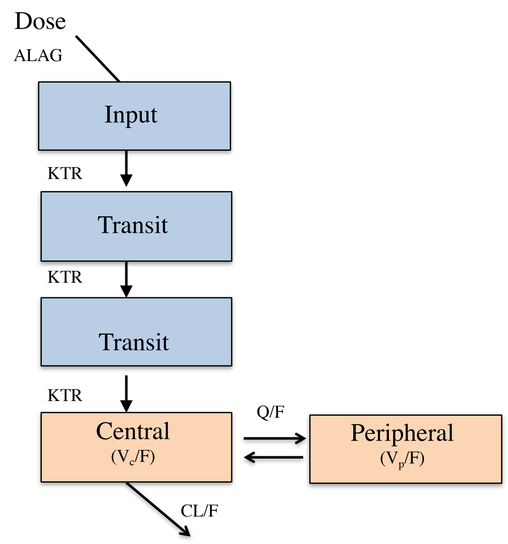
Population PK Model

- The PK of SAM in healthy and MDD subjects following single and multiple doses of SL ALKS 5461 was described by a 2-compartment disposition model, linear elimination, and absorption via a series of transit compartments.

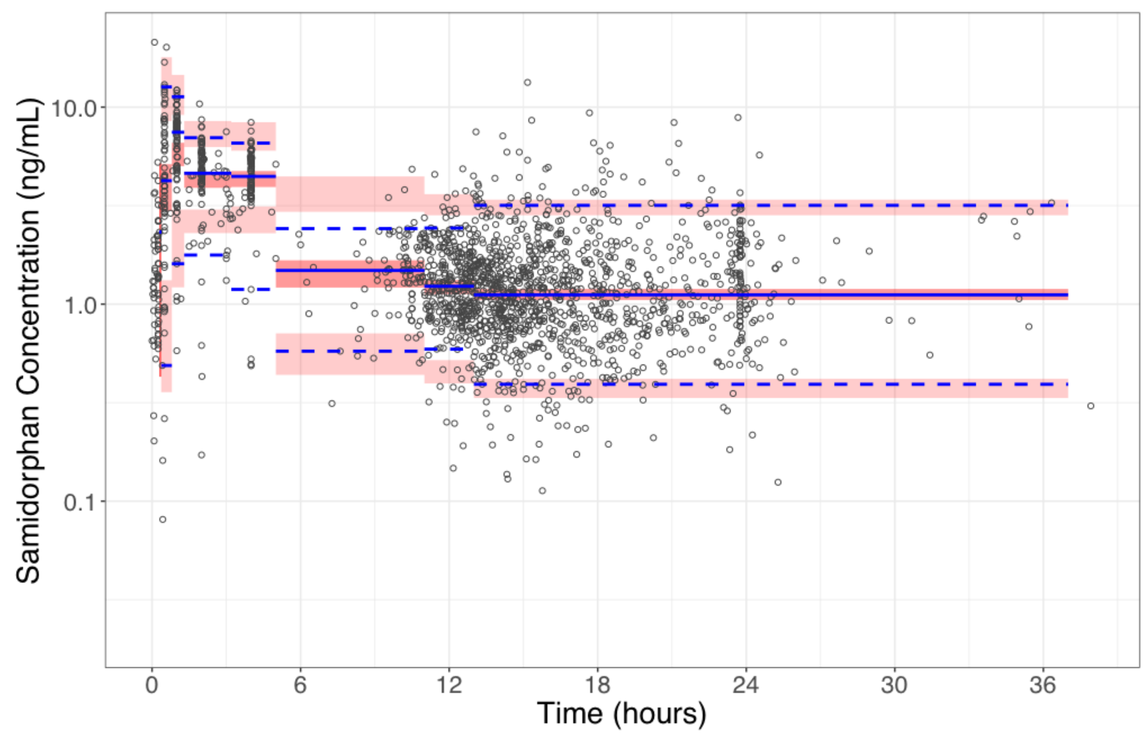


- An additive residual error model on log transformed data was included to account for the increased variability observed during the absorption phase.

Parameter Estimates for the Final SAM Model

Parameter	Estimate (%RSE)
Apparent Clearance (CL/F, L/hr)	45.3 (1.7)
Percentage Decrease in CL for Phase II (%)	15.1 (29.9)
Percentage Decrease in CL for Phase III (%)	31.0 (6.5)
Exponent for CrCL on CL	0.36 (4.3)
Percentage Decrease in CL for Severe or Moderate Hepatic Impairment (%)	41.4 (13.8)
Apparent Central Volume of Distribution (V_c/F, L)	383 (2.8)
Apparent Inter-compartmental Clearance (Q/F, L/hr)	13.6 FIX
Apparent Peripheral Volume of Distribution (V_p/F, L)	81.9 (6.1)
Exponent for LBW on V_c	0.46 (28.2)
Absorption Transit Rate (KTR, hr^{-1})	6.43 FIX
Absorption Transit Rate for Severe or Moderate Hepatic Impairment (KTR, hr^{-1})	10.3 (21.7)
Lag-time for Study ALK33BUP-201 ($ALAG_{201}$, min)	10.6 FIX
Lag-time (ALAG, min)	7.4 FIX
Power Function (COV) on Relative Bioavailability (F)	0.0713 FIX
Covariance Between CL/F and V_c/F	0.0497 (11.7)
Between Subject Variability CL/F (σ^2)	0.0792 (5.3)
Between Subject Variability V_c/F (σ^2)	0.0646 (14.1)
Between Subject Variability ALAG (σ^2)	0.2331 (12.4)
Between Subject Variability RUV (σ^2)	0.3752 (7.5)
Between Occasion Variability KTR (σ^2)	0.3886 (6.2)
RUV for Time Since Last Dose $\leq$ 1.5 hour (σ^2)	0.049 (7.6)
RUV for Time Since Last Dose $>$ 1.5 hour (σ^2)	0.0126 (7.0)
RUV in Phase II/III Studies (σ^2)	0.2334 (4.5)

Prediction Corrected Visual Predictive Check



Open circles = individual observed, dashed blue lines = observed 5th & 95th percentiles, solid blue line = observed median, shaded red areas = 90% prediction interval for the 5th, median, and 95th percentiles. Note: both the x- and y-axis are on a log scale.

Covariate Effects

- Patient intrinsic factors such as age, race, and the concomitant administration of antidepressant therapy (ADT) had no effect on the PK of SAM.
- Sex, lean body weight, patient status, and formulation were included as covariates in the final model but resulted in no clinically significant impact on exposure.
- Subjects with severe renal impairment and hepatic impairment showed increased SAM exposure and were accounted for by the covariate model.
- Simulations indicated that mild to moderate renal impairment did not result in clinically relevant changes in SAM exposure.

Fold change in AUCτ