A Population Pharmacokinetic Model of Buprenorphine 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 (BUP) 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 BUP.
- No population PK models exist in the literature following SL administration of BUP in adults.

Aim

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

Methods

- Data from 10 studies (healthy volunteers (HV), 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 BUP exposure.

Conclusions

- A population PK model for BUP following SL administration of ALKS 5461 was developed that adequately described the PK of BUP in healthy subjects and MDD patients.
- Age, weight, gender, race, or concomitant treatment of ADTs showed no effect on the PK of BUP in ALKS 5461.
- The increased BUP 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 BUP in ALKS 5461.

References

1. Fava M. Am J Psychiatry. 2016 May 1;173(5):499-508.
2. Chan PLS. Br J Clin Pharmacol, 65 Suppl 1:76-85,Apr2008

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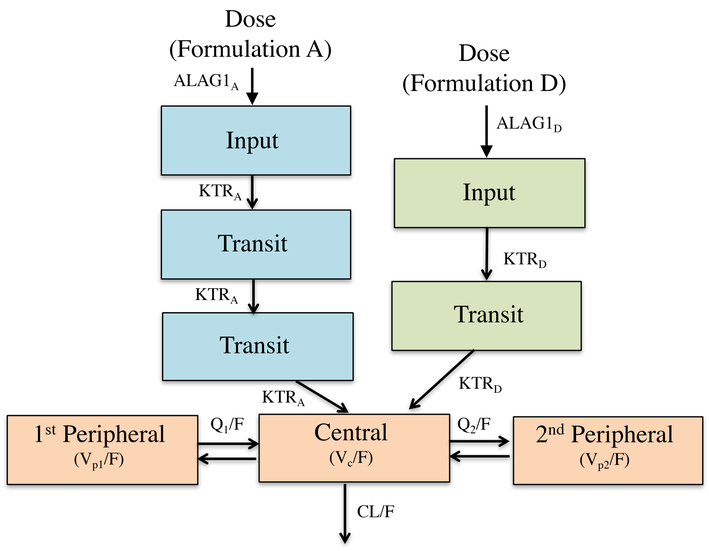
Population PK Model

- The PK of BUP in healthy and MDD subjects following single and multiple doses of SL ALKS 5461 was described by a 3-compartment disposition model, linear elimination, and absorption via a series of transit compartments.

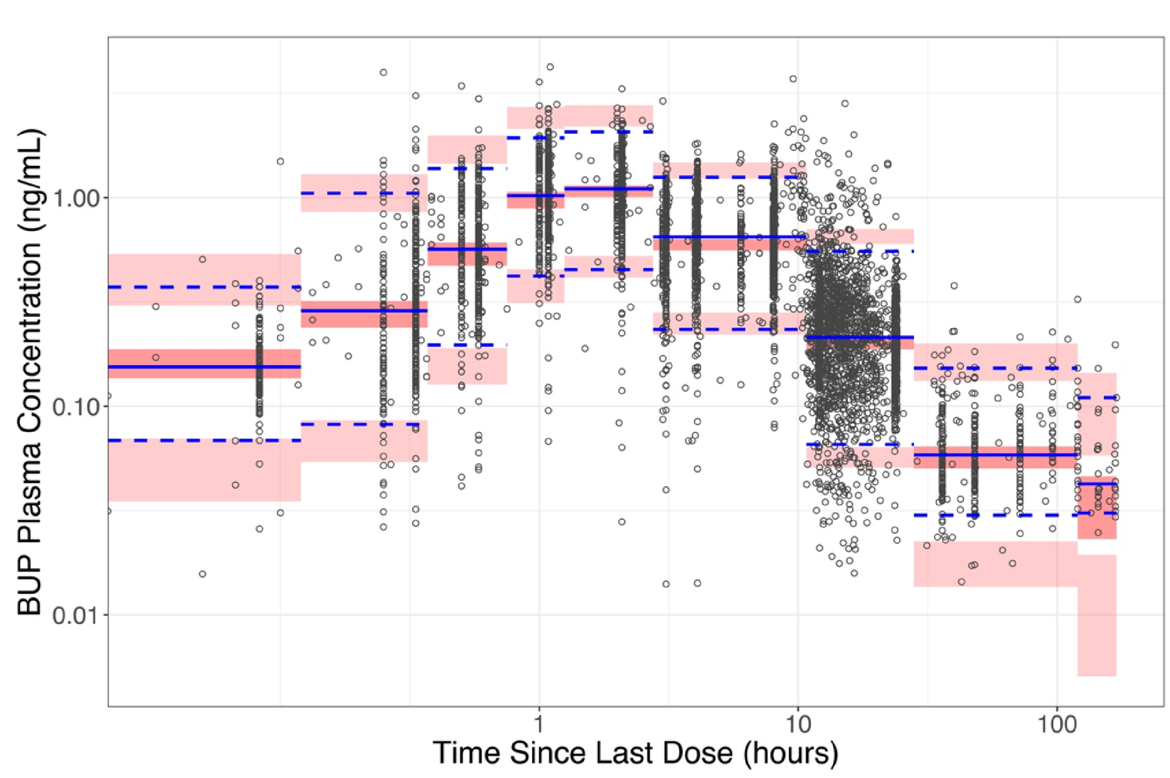


- An additive residual error model on log transformed data was included with a time dependent weight applied to account for the increased variability observed during the absorption phase.[2]

Parameter estimates for the final BUP model

Parameter	Estimate (%RSE)
Apparent Clearance (CL/F, L/hr)	178 (5.0)
Decrease in CL in MDD Patients (%)	11.6 (4.9)
Decrease in CL in Severe Renal Impairment (%)	21.2 (12.9)
Decrease in CL in Moderate Hepatic Impairment (%)	39.9 (28.2)
Decrease in CL in Severe Hepatic Impairment (%)	65.5 (18.5)
Increase in CL for Males (%)	15 (4.1)
Apparent Central Volume of Distribution (V_c/F, L)	1250 (4.4)
Increase in V_c in Moderate / Severe Hepatic Impairment (%)	34 (14.7)
Severe Hepatic Impairment (%)	34 (14.7)
Exponent for LBW on V_c	0.391 (25.8)
Apparent 1st Inter-compartmental Clearance (Q_1/F, L/hr)	132 (9.6)
Apparent 1st Peripheral Volume of Distribution (V_{p1}/F, L)	1560 (17.9)
Apparent 2nd Inter-compartmental Clearance (Q_2/F, L/hr)	103 (13.5)
Apparent 2nd Peripheral Volume of Distribution (V_{p2}/F, L)	5150 (10.2)
Absorption Transit Rate for Formulation A (KTR_A, hr^{-1})	5.59 (7.4)
Absorption Transit Rate for Formulation D (KTR_D, hr^{-1})	2.02 (4.9)
Increase in KTR for Hepatic Impairment Subjects (%)	116 (10.9)
Lag-time for Formulation A ($ALAG1_A$, min)	7.56 (6.6)
Lag-time for Formulation D ($ALAG1_D$, min)	4.1 (26.3)
Bioavailability (F)	1 FIXED
Decrease in F if Multiple Tablets Administere	14.9 (3.2)
Increase in F for Studies ALK5461-A108, ALK5461-A109, & ALK5461-215	56 (7.0)
Increase in F in Severe Renal Impairment (%)	50 (12.9)
Increase in F in Mild / Moderate Hepatic Impairment (%)	45 (7.8)
Correlation Between CL/F and V_c/F	0.56 (8.1)
Between Subject Variability CL/F (CV%)	36.3 (5.6)
Between Subject Variability V_c/F (CV%)	33.8 (6.6)
Between Subject Variability KTR (CV%)	34.6 (7.5)
Between Occasion Variability F (CV%)	41.8 (4.2)
Maximum Change of RUV above the Base-line (P_{MAX}, CV%)	37.2 (11.3)
Time of Maximum RUV ($T_{MAX,RUV}$, min)	20.6 (6.0)
Rate Constant for the Time Course of RUV (K_{RUV}, hr^{-1})	11.3 (24.2)
Base RUV (CV%)	15.0 (4.1)
Base RUV for Selected Subjects ($Base_{Selected}$, CV%)	27.9 (7.6)
RUV in Phase III Studies ($RUV_{PhaseIII}$, CV%)	53.6 (5.4)

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 BUP.
- 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 BUP 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 BUP exposure.

Fold change in AUCτ