Population Pharmacokinetics of Olanzapine and Samidorphan When Administered in Combination in Healthy Subjects and Patients With Schizophrenia

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All authors designed the research. L.S., R.M. and B.M.S. performed the research. R.M. analysed the data. All authors contributed to the drafting, critical review, and revision of the manuscript. All authors granted approval of the final manuscript for submission.

Declaration of Conflicting Interests
L.S. and B.R. are employees of Alkermes, Inc. R.M. and B.M.S. are employees of ICON. All authors met the ICMJE and GPP3 authorship criteria.

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Data Sharing Statement

The data collected in this study are proprietary to Alkermes, Inc. Alkermes, Inc. is committed to public sharing of data in accordance with applicable regulations and laws.
ABSTRACT

A combination of olanzapine and samidorphan (OLZ/SAM) is in development for treatment of patients with schizophrenia or bipolar I disorder. Population pharmacokinetic (PopPK) models for olanzapine and samidorphan were developed using data from 11 clinical studies in healthy subjects or patients with schizophrenia. A 2-compartment disposition model with first-order absorption and elimination and a lag time for absorption adequately described concentration-time profiles of both olanzapine and samidorphan. Age, sex, race, smoking status, and body weight were identified as covariates that impacted the pharmacokinetics of olanzapine. A moderate effect of body weight on samidorphan pharmacokinetics was identified by the model but was not considered clinically meaningful. The effects of food, hepatic or renal impairment, and coadministration with rifampin on the pharmacokinetics of olanzapine and samidorphan, as estimated by the PopPK analysis, were consistent with findings from dedicated clinical studies designed to evaluate these specific covariates of interest. Food intake did not have a clinically relevant effect on the pharmacokinetics of olanzapine or samidorphan. Consistent with the known metabolic pathways for olanzapine (primarily via uridine 5’-diphospho-glucuronosyltransferase [UGT]–mediated direct glucuronidation and cytochrome P450 [CYP]–mediated oxidation) and for samidorphan (predominately mediated by CYP3A4), coadministration of OLZ/SAM with rifampin, a strong inducer of CYP3A4 and an inducer of UGT enzymes, significantly decreased the systemic exposure of both olanzapine and samidorphan. Severe renal impairment or moderate hepatic impairment resulted in modest increase in olanzapine and samidorphan exposure.

Keywords: Covariates, antipsychotic; bipolar I disorder; opioid antagonist; pharmacokinetics; population pharmacokinetics; schizophrenia
INTRODUCTION

The atypical antipsychotic olanzapine has been in use for the last 20 years and provides an effective treatment option for patients with schizophrenia or bipolar I disorder.\textsuperscript{1-7} Because the two disorders typically require lifelong pharmacologic management, tolerability is of paramount importance. Although olanzapine is considered to be one of the most effective atypical antipsychotic agents, its clinical utility has been limited by weight gain and metabolic effects associated with its use.\textsuperscript{8}

One potential strategy that has emerged in the management of olanzapine-associated weight gain involves targeting the endogenous opioid system, which plays a role in weight gain and metabolism.\textsuperscript{9-12} A combination of olanzapine and samidorphan (OLZ/SAM) is in development for the treatment of patients with schizophrenia or bipolar I disorder. Samidorphan is a new molecular entity that acts as an opioid receptor antagonist\textsuperscript{13-15} The addition of samidorphan to olanzapine is intended to mitigate olanzapine-associated weight gain while preserving the antipsychotic efficacy of olanzapine. Data from completed clinical studies indicated that treatment with OLZ/SAM (olanzapine 5–20 mg in combination with samidorphan 5–20 mg) and olanzapine (5–20 mg) resulted in similar improvements in antipsychotic symptoms,\textsuperscript{16,17} but treatment with OLZ/SAM resulted in significantly less weight gain compared with olanzapine.\textsuperscript{16,18,19}

The pharmacokinetics of olanzapine and of samidorphan have been evaluated after oral administration of either compound alone or in combination.\textsuperscript{18-28} Pharmacokinetic parameters of olanzapine and samidorphan when administered in combination as OLZ/SAM\textsuperscript{23-28} were comparable with previously published data when each component was administered alone,\textsuperscript{20,21} indicating that combining olanzapine with samidorphan does not affect the pharmacokinetics of either component. In addition, food intake did not have a clinically relevant impact on the rate and extent of olanzapine and samidorphan absorption.\textsuperscript{24} Consistent with the known metabolic pathways for olanzapine (primarily via uridine 5′-diphospho-glucuronosyltransferase [UGT]–mediated direct glucuronidation and cytochrome P450 [CYP]–mediated oxidation) and samidorphan (predominately mediated by CYP3A4),\textsuperscript{21,29,30} systemic exposures to both olanzapine and samidorphan were decreased when OLZ/SAM was coadministered with rifampin, a strong cytochrome P450 (CYP) 3A4 inducer and an inducer of UGT enzymes.\textsuperscript{25} Modest increases in olanzapine and samidorphan exposures were observed in subjects with moderate hepatic impairment or severe renal impairment.\textsuperscript{26} The objectives of the current analyses were to develop population pharmacokinetic (PopPK) models for olanzapine and samidorphan that describe plasma concentration versus time profiles of each compound, to identify covariates that contribute to the interindividual variability of olanzapine and samidorphan pharmacokinetic parameters, and to quantify the impact of intrinsic and extrinsic factors on the steady-state exposures of olanzapine and samidorphan after oral administration of OLZ/SAM.
METHODS

Data sources and software
Each study contributing to this analysis was conducted in accordance with the Declaration of Helsinki and with the International Council for Harmonisation Good Clinical Practice Guidelines. Study protocols, amendments, and informed consent forms were reviewed by each clinical site’s independent ethics committee or institutional review board prior to any subject being enrolled. All subjects provided written informed consent before study participation. The final PopPK models for olanzapine and samidorphan included concentration-time data from 10 studies of OLZ/SAM (9 phase 1 studies with intense sampling and 1 phase 3 study with sparse sampling) in healthy subjects and in patients with schizophrenia (Table S1). One additional phase 1 study of samidorphan alone was also included in the final PopPK model for samidorphan.

Data were pooled and analyzed by nonlinear mixed-effects modeling using NONMEM software (v7.3.0). Simulated bioequivalence derivations, data presentation, and construction of plots were generated using R (v3.4.0), Excel (v2016), and Phoenix WinNonlin (v8) software, as appropriate.

Pharmacokinetic assay
Except for the one samidorphan alone study (Table S1), plasma concentrations of olanzapine and samidorphan were analyzed using a validated liquid chromatography system coupled with detection by tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 0.250 ng/mL for both olanzapine and samidorphan. For the samidorphan alone study, plasma concentrations of samidorphan were analyzed using a validated LC-MS/MS method with an LLOQ of 0.250 ng/mL.

Model development
PopPK model development consisted of establishing a base model and a final model for olanzapine and samidorphan separately. Base models were informed by the first 5 completed studies that covered the intended therapeutic doses of OLZ/SAM, obtained from both healthy subjects and patients with schizophrenia. A previously described PopPK model for olanzapine, a 2-compartment model with first-order absorption and elimination, served as the starting point for olanzapine model development. Primary base models for both olanzapine and samidorphan were selected that appropriately describe the plasma concentration versus time profiles of each compound observed in these clinical studies. Structural and variance model parameters were estimated for the base models, which were then expanded and re-estimated to include final data.
from additional studies. Subjects treated with placebo were not included in the PopPK analysis. Models were fitted via Monte Carlo importance sampling expectation maximization assisted by mode a posteriori (IMPMAP) method with an ISAMPLE of 500. The following were the settings for the $EST steps for both olanzapine and samidorphan:

$EST METHOD=IMPMAP NUMERICAL SLOW INTER EONLY=0 NITER=1000 ISAMPLE=500 PRINT=1 SIGL=6 NSIG=2 NOPRIOR=1 NOHABORT FNLETA=0 CTYPE=2 CITER=10 CINTERVAL=1 RANMETHOD=32 SEED=11455 MCETA=10.

IMP was selected as the estimation method, as FOCEI was associated with problems completing the covariance step. Additionally, comparable results were obtained between IMP and IMPMAP. An ISAMPLE=500 was sufficient to achieve both model optimization and good precision on parameter estimates. M3 methodology was used, allowing for postdose concentrations below the lower limit of quantification to be included in the analysis.

Interindividual variability was incorporated exponentially, as described by the equation:

$$\ln(P_i) = \ln(\text{TV}_P) + \eta_{i_P}$$

where \(P_i\) is the expected distribution of the individual parameter values, \(\text{TV}_P\) is the typical population value, and \(\eta_{i_P}\) is the random quantity at the individual level. For residual variability, differences between observed data \((Y_{\text{obs}})\) and model predictions of the dependent variable \((Y_{\text{pred}})\) were regarded as random quantities and were modeled in terms of epsilon (\(\varepsilon\)) variables, as follows:

$$Y_{\text{obs},ij} = Y_{\text{pred},ij} \cdot (1 + \varepsilon_{1ij})$$

where \(Y_{\text{obs},ij}\) is the \(j^{th}\) observed value of the dependent variable in the \(i^{th}\) individual, \(Y_{\text{pred},ij}\) is the \(j^{th}\) predicted value of \(Y\) in the \(i^{th}\) individual, and \(\varepsilon_{1ij}\) describes the difference between \(Y_{\text{obs},ij}\) and \(Y_{\text{pred},ij}\) (with a mean of zero and variance of \(\sigma_1^2\)).

Baseline demographic covariates examined in the models included age, sex, race, participant type (ie, healthy volunteer or patient with schizophrenia), body weight, lean body weight, body mass index (BMI), and BMI category (\(\leq 25\) kg/m\(^2\) or >25 kg/m\(^2\)). The clinical laboratory covariates examined included serum albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Total bilirubin, estimated creatinine clearance (CRCL) based on the Cockcroft-Gault equation, and estimated glomerular filtration rate (eGFR) based on a Modification of Diet in Renal Disease equation were also assessed for inclusion. Additional covariates including formulation (OLZ/SAM bilayer tablet or tablet of olanzapine or samidorphan), renal function (normal; mild, moderate, or severe renal impairment) as measured by CRCL or eGFR, and dose were assessed. Furthermore, the effects of coadministration with rifampin or in the presence of moderate hepatic or severe renal impairment as evaluated in the phase 1 clinical organ impairment studies were examined. Lastly, smoking status (nonsmoker, not recorded, or smoker), food status (fed and fasted), and effects of concomitant CYP inducers or inhibitors of CYP3A4 or CYP1A2 were also evaluated. Covariate selection for inclusion in the model was based on 1 or more of the following criteria: plots of individual estimates \((P_i)\) versus covariates demonstrated a trend, a statistically significant covariate effect as determined by univariate analysis of variance or regression analysis (for categorical and continuous covariates, respectively), a physiological or pharmacological rationale, or information from prior analyses or published sources.
The effects of covariates on model parameters were assessed using a full covariate model, with backwards elimination approach. A covariate was considered statistically significant when its deletion from the full model increased the objective function value (OFV) less than 10.83 points (p=0.001; degree of freedom=1). The magnitudes of the effects of significant covariates on associated model parameters were assessed over relevant ranges (eg, minimum and maximum values in the data set); confidence intervals were also calculated.

Continuous covariates (COV) were centered at their typical values (TV_COV), with TV_P expressed as:

\[
\ln(TV_P) = \ln(\theta_P) + \theta_{COV,P} \cdot \ln \left( \frac{COV}{TV_COV} \right),
\]

where \( \theta_P \) is the estimated parameter representing the typical value of model parameter \( P \) when the individual covariate (COV) is equal to TV_COV and \( \theta_{COV,P} \) is the estimated parameter representing the influence of covariate COV on model parameter \( P \). For categorical covariates, each category must have been represented in at least 10% of the population in order to be evaluated. Categorical covariates (CAT) were tested and incorporated in the model as a series of index variables taking on values of zero or one. Index variables were included in the model according to the following equation:

\[
\ln(TV_P) = \ln(\theta_P) + \text{CAT}_{1i} \cdot \ln(\theta_{CAT_{1i},P}),
\]

where \( \theta_P \) is the estimated parameter representing the typical value of model parameter \( P \) when the individual categorical covariate index variable (CAT_{1i}) is equal to zero, and \( \theta_{CAT_{1i},P} \) is the estimated parameter representing the relative influence of categorical covariate index variable on model parameter \( P \) when CAT_{1i} is equal to one.

**Model evaluation**

Model goodness-of-fit was assessed by a variety of plots and computed metrics. Goodness-of-fit plots of the observed versus model-predicted concentrations and individual weighted residuals versus population predictions and time since last dose were examined for departures from linearity and homoscedasticity, which were diagnostic of model misspecifications. Change in OFV (\( \Delta \text{OFV} \)) was also evaluated to compare competing hierarchical models. \( \Delta \text{OFV} \) required for a given probability was adjusted with stochastic estimation methods (eg, IMPMAP). Simulations from posterior prediction-corrected visual predictive checks (pcVPC) were used to evaluate whether the final models and associated parameters were consistent with observed data.

**Model application**

The final PopPK models were applied to predict the impact of significant covariates on steady-state exposures of olanzapine and samidorphan. For each covariate and reference individual, 500 steady-state plasma concentration-time profiles were simulated following once-daily administration of OLZ/SAM 10 mg/10 mg; maximum concentration (\( C_{\text{max,ss}} \)) and area under the curve during a daily dosing interval (\( \text{AUC}_{\text{tau}} \)) were derived. Each “covariate individual” was compared with the reference individual using a standard analysis of variance bioequivalence approach (Phoenix WinNonlin). Simulated \( C_{\text{max,ss}} \) and \( \text{AUC}_{\text{tau}} \) outputs are presented as forest plots.
RESULTS

The final PopPK model for olanzapine included 601 evaluable subjects contributing 9905 concentration records; a total of 5.6% of the olanzapine concentrations were below the LLOQ. The final PopPK model for samidorphan included 521 subjects with 9321 concentration records; a total of 11.5% of the samidorphan concentrations were below the LLOQ. Summarized demographic and clinical characteristics for the subjects included in the final PopPK models are presented in Table 1.

Subjects included in the final olanzapine data set had a median age of 36 years, with a median BMI of 25.5 kg/m²; subjects included in the final samidorphan data set had a median age of 34 years, with a median BMI of 25.6 kg/m².

The final PopPK models for olanzapine and samidorphan were both a 2-compartment disposition model with first-order absorption and elimination and a lag time for absorption (Figure S1). The model contained 6 structural parameters (rate of absorption [Ka], lag time for absorption [ALAG], apparent clearance [CL/F], apparent volume of central compartment [Vc/F], apparent volume of peripheral compartment [Vp/F], and intercompartmental clearance [Q/F]). The final olanzapine PopPK model contained 10 covariates, which consisted of 3 continuous covariates (body weight on CL/F, body weight on Vc/F, and age on Vc/F) and 7 categorical covariates (Table 2). The final samidorphan PopPK model contained 8 covariates, which consisted of 2 continuous covariates (body weight on CL/F, body weight on Vc/F) and 6 categorical covariates (Table 2).

Key parameter estimates for the final olanzapine and samidorphan PopPK models are presented in Tables 3 and 4, respectively. In the final olanzapine model, several components were fixed rather than estimated (ie, ALAG was fixed at 0.782 h; interindividual variability for Vp/F and Q/F were fixed at 50% to reduce model instability and minimize stochastic noise in OFV). The final olanzapine model contained covariate effects for body weight on CL/F and Vc/F (fixed at theoretical allometric exponents of 0.75 and 1.0, respectively) and for the effect of moderate hepatic impairment on CL/F, which was fixed at a 12% reduction based on the observed effect in a clinical study.26 Model estimates of CL/F and Vc/F for olanzapine were 15.5 L/h and 656 L, respectively. The interindividual variability for CL/F and Vc/F was estimated at 43.2% and 35.6%, respectively. In the final samidorphan model, the interindividual variability for Q/F was fixed at 50% to reduce model instability and minimize stochastic noise in OFV. The model contained covariate effects for body weight on CL/F and Vc/F, fixed at theoretical allometric exponents of 0.75 and 1.0, respectively. The model-derived CL/F and Vc/F for samidorphan were 35.4 L/h and 297 L, respectively, with interindividual variability for CL/F and Vc/F estimated at 29.4% and 23.3%.

The final models were evaluated by goodness-of-fit plots and pcVPC.
Goodness-of-fit plots of the final olanzapine and samidorphan models (Figure 1A and 1B, respectively) indicated that observed concentrations were well described by the model predictions. Based on stratified versions of these plots, there is no apparent prediction bias due to study or dose effect observed (data not shown). By pcVPC, the majority of observed olanzapine and samidorphan concentrations were contained within the final PopPK model–predicted 90% prediction intervals (Figure 2A and 2B), indicating the final models adequately described the PopPK of olanzapine and samidorphan. The models described observed olanzapine and samidorphan concentrations well across the doses (5–30 mg for both olanzapine and samidorphan) and study populations (healthy subjects and patients with schizophrenia) evaluated in clinical studies, indicating the pharmacokinetics of both olanzapine and samidorphan were linear across the clinical dose range, with no notable difference between healthy subjects and patients with schizophrenia.

Application of the final PopPK models for the prediction of the effects of significant covariates on steady-state exposure (C_{max,ss} and AUC_{tau}) of olanzapine and samidorphan indicated that olanzapine exposure was affected by age, sex, race, smoking, and body weight (Figure 3A and 3B). Samidorphan exposure was not affected by age, sex, race, or smoking. A modest impact of body weight on samidorphan exposure was predicted (ratio of AUC_{tau} of 1.39 to 0.60 over the range of 44 to 141 kg [relative to 70 kg]) but was not considered clinically meaningful (Figure 3C and 3D).

**DISCUSSION**

In this analysis, data from more than 500 healthy subjects and patients with schizophrenia were used to develop PopPK models for olanzapine and samidorphan that allowed for the determination of population characteristics that influenced the pharmacokinetic parameters of each compound across several doses, including the intended therapeutic dose range of OLZ/SAM. The final PopPK models for olanzapine and samidorphan were both a 2-compartment disposition model with first-order absorption and elimination and a lag time for absorption. These models adequately described observed olanzapine and samidorphan concentrations and indicated linear pharmacokinetics for both compounds across the 5- to 30-mg dose range studied. These results are consistent with previously published PopPK analyses for olanzapine\(^{20,31,37}\) and phase 1 studies with samidorphan.\(^{21,22}\)

The current analysis, conducted using data from clinical studies with the combination product OLZ/SAM, confirmed that the addition of samidorphan did not alter the pharmacokinetics of olanzapine, which supports the clinical findings that samidorphan mitigated olanzapine-associated weight gain while preserving the antipsychotic efficacy of olanzapine. Generally, the covariates identified here using the final PopPK models (ie, compartmental analyses) were consistent with published data and individual studies evaluating specific covariates of interest (eg, hepatic or renal impairment, food effect). However, as discussed below, the exact magnitudes of the covariate effects based on PopPK analysis were not identical to those published results analyzed by model-
independent computations (ie, noncompartmental analysis). These differences may be explained by the larger number of subjects in the PopPK analysis (pooled studies with different designs and populations) and associated greater variability than in individual clinical studies. As such, the differences in the exact magnitudes of the covariate effects did not result in any changes in dosing recommendations based on the results from individual studies evaluating specific covariates of interest.

The current PopPK analysis indicated that the pharmacokinetics of olanzapine, including population estimates of CL/F, were affected by age, sex, race, smoking, and body weight, consistent with published data for olanzapine.\textsuperscript{20,37,38} In one published PopPK analysis, olanzapine CL/F was found to be higher in black subjects (26% higher than nonblack subjects) and in smokers (55% higher than nonsmokers), and lower in women (38% lower than men).\textsuperscript{38} In the current analysis, the final olanzapine PopPK model indicated higher CL/F in black subjects (10% higher than non-black subjects) and smokers (30% higher than non-smokers; including 29% of subjects with missing smoking status), and a 14% lower CL/F in women than in men (Table 3). However, given the wide therapeutic range of olanzapine plasma concentrations\textsuperscript{39} and the wide PopPK variability of olanzapine, dose modifications based on sex, race, and smoking status are generally not needed.\textsuperscript{20,40} In addition, a meta-analysis suggested that treatment with olanzapine was efficacious, regardless of a patient’s age, sex, race, and smoking habits.\textsuperscript{41} Body weight was identified as a significant covariate in the final PopPK model for olanzapine, which is consistent with a published PopPK analysis for olanzapine.\textsuperscript{37} However, the magnitude of change in olanzapine exposure due to body weight is predicted to be small (ie, the ratio of C\textsubscript{max} ranged from 0.59 to 1.46 and the ratio of AUC\textsubscript{tau} ranged from 0.61 to 1.43 over the weight range of 44 to 141 kg, relative to the reference of 70 kg [Figure 3A and 3B]). Again, given the wide therapeutic range of olanzapine plasma concentrations\textsuperscript{39} and the wide PopPK variability of olanzapine, these small changes due to body weight are not considered clinical meaningful.

The effects of hepatic and renal impairment on the pharmacokinetics of olanzapine, as estimated by the current PopPK analysis, were consistent with findings observed in clinical studies specifically designed to evaluate the effects of these covariates. In a clinical study evaluating the impact of hepatic impairment, the area under the plasma concentration-time curve from time 0 to infinity (AUC\textsubscript{\textinfty}) of olanzapine following a single dose of OLZ/SAM was 1.7-fold higher in subjects with moderate hepatic impairment relative to healthy, age- and sex-matched controls.\textsuperscript{26} In the current PopPK analysis, steady-state AUC\textsubscript{tau} of olanzapine was predicted to be 1.16-fold higher in subjects with moderate hepatic impairment compared with subjects with normal hepatic function (Figure 3B), which understated the effect relative to the results observed in the clinical study. In subjects with severe renal impairment, the CL/F of olanzapine decreased 33% relative to healthy, age- and sex-matched controls.\textsuperscript{26} The final PopPK model here estimated a 20% decrease in olanzapine CL/F in subjects with severe renal impairment (Table 3). Given that the interindividual variabiliity estimate of CL/F was 43% in the final olanzapine model, the estimated effect based on PopPK analysis was considered comparable to that observed in the clinical study.
The final PopPK model for olanzapine predicted a 1.8-fold higher olanzapine CL/F in the presence of rifampin (Table 3), which is comparable to the 1.9-fold higher CL/F reported in a clinical drug-drug interaction study.\textsuperscript{25} Similarly, the final PopPK model for olanzapine estimated a 6% reduction in olanzapine bioavailability for subjects in a fed state compared with those who were fasted (Table 3), consistent with the 7% reduction reported in a clinical food effect study.\textsuperscript{24}

Body weight, as with olanzapine, was identified as a significant covariate in the final PopPK model for samidorphan; however, the magnitude of change in samidorphan exposure due to body weight difference is predicted to be up to 49% (ie, the ratio of C\textsubscript{max} ranged from 0.52 to 1.49 and the ratio of AUC\textsubscript{tau} ranged from 0.60 to 1.39 over the weight range of 44 to 141 kg, relative to the reference of 70 kg [Figure 3C and 3D]) and is not considered clinically meaningful, based on the known exposure-response relationship for samidorphan on mitigation of weight gain.\textsuperscript{16,19} In addition, the model estimated the effects of covariates (ie, moderate hepatic impairment, severe renal impairment, inducer effect of rifampin, food effect) that had been assessed in clinical studies.\textsuperscript{24-26} In a clinical study evaluating the impact of hepatic impairment, samidorphan AUC\textsubscript{∞} following a single dose of OLZ/SAM was 1.5-fold higher in subjects with moderate hepatic impairment compared with healthy, age- and sex-matched controls.\textsuperscript{26} Consistent with the results observed in the clinical study, the final samidorphan PopPK model predicted a 1.23-fold higher steady-state AUC\textsubscript{tau} of samidorphan following once daily administration of OLZ/SAM (Figure 3D). The final samidorphan PopPK model also predicted a 43% reduction in samidorphan CL/F in subjects with severe renal impairment (Table 4), consistent with a 56% reduction observed in the clinical study.\textsuperscript{26}

The final PopPK model for samidorphan predicted a 2.7-fold higher samidorphan CL/F in the presence of rifampin (Table 4), which is consistent with a 3.7-fold higher samidorphan CL/F observed in the clinical study.\textsuperscript{25} Furthermore, simulations from the final samidorphan PopPK model estimated a 29% reduction in steady-state C\textsubscript{max} of samidorphan for subjects in the fed state compared with those who were fasted, which is higher than the 15% reduction reported in a clinical food effect study with OLZ/SAM.\textsuperscript{24}

At initiation, olanzapine is typically titrated to improve tolerability, and the maintenance dose required is based on the individual patient’s clinical response. Patient-level covariate effects may help predict the final maintenance dose, and interindividual variation may provide another rationale for up-titration, but both would have minimal impact on current clinical practice. Covariate effects may be more meaningful in helping physicians to anticipate the need for a change in the maintenance dose when the value of a covariate changes for a given patient over time (eg, initiation or discontinuation of smoking, requirement of concomitant medications such as rifampin, or development of renal or hepatic impairment).

In conclusion, PopPK models for olanzapine and samidorphan were developed based on data from phase 1 and phase 3 studies. Covariates that described interindividual variability in pharmacokinetic parameters were identified and incorporated into the models. Age, sex, race, smoking status, and body weight were identified as covariates that impacted the pharmacokinetics of olanzapine, consistent with published data for olanzapine. Pharmacokinetics of samidorphan was
not affected by age, sex, race, or smoking status. A modest effect of baseline body weight on samidorphan exposure was identified by the model but was not considered clinically meaningful. Finally, the effects of food, hepatic or renal impairment, and coadministration with rifampin on the pharmacokinetics of olanzapine and samidorphan, as estimated by the PopPK analysis, were consistent with the findings from dedicated phase 1 studies designed to evaluate these specific covariates of interest.
REFERENCES

1. Zyprexa [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.

2. Zyprexa [original package insert]. Indianapolis, IN: Eli Lilly and Company; 1996.

3. Lopez-Munoz F, Shen WW, D’Ocon P, Romero A, Alamo C. A history of the pharmacological treatment of bipolar disorder. *Int J Mol Sci.* 2018;19(7):2143.

4. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353(12):1209-1223.

5. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382(9896):951-962.

6. Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. *Psychol Med.* 2015;45(2):299-317.

7. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet.* 2011;378(9799):1306-1315.

8. Berkowitz RL, Patel U, Ni Q, Parks JJ, Docherty JP. The impact of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) on prescribing practices: an analysis of data from a large midwestern state. *J Clin Psychiatry.* 2012;73(4):498-503.

9. Czyzyk TA, Romero-Pico A, Pintar J, et al. Mice lacking delta-opioid receptors resist the development of diet-induced obesity. *Faseb J.* 2012;26(8):3483-3492.

10. Czyzyk TA, Nogueiras R, Lockwood JF, et al. Kappa-opioid receptors control the metabolic response to a high-energy diet in mice. *Faseb J.* 2010;24(4):1151-1159.

11. Tabarin A, Diz-Chaves Y, Carmona Mdel C, et al. Resistance to diet-induced obesity in mu-opioid receptor-deficient mice: evidence for a "thrifty gene". *Diabetes.* 2005;54(12):3510-3516.

12. Gallagher CJ, Gordon CJ, Langefeld CD, et al. Association of the mu-opioid receptor gene with type 2 diabetes mellitus in an African American population. *Mol Genet Metab.* 2006;87(1):54-60.
13. Shram MJ, Silverman B, Ehrich E, Sellers EM, Turncliff R. Use of remifentanil in a novel clinical paradigm to characterize onset and duration of opioid blockade by samidorphan, a potent mu-receptor antagonist. *J Clin Psychopharmacol.* 2015;35(3):242-249.

14. Wentland MP, Lou R, Lu Q, et al. Syntheses of novel high affinity ligands for opioid receptors. *Bioorg Med Chem Lett.* 2009;19(8):2289-2294.

15. Bidlack JM, Knapp BI, Deaver DR, et al. In vitro pharmacological characterization of buprenorphine, samidorphan, and combinations being developed as an adjunctive treatment of major depressive disorder. *J Pharmacol Exp Ther.* 2018;367(2):267-281.

16. Martin WF, Correll CU, Weiden PJ, et al. Mitigation of olanzapine-induced weight gain with samidorphan, an opioid antagonist: a randomized double-blind phase 2 study in patients with schizophrenia. *Am J Psychiatry.* 2019;176(6):457-467.

17. Potkin SG, Kunovac J, Silverman BL, et al. Efficacy and safety of a combination of olanzapine and samidorphan in adult patients with an acute exacerbation of schizophrenia: outcomes from the randomized, phase 3 ENLIGHTEN-1 study. *J Clin Psychiatry.* 2020;81(2):19m12769.

18. Silverman BL, Martin W, Memisoglu A, DiPetrillo L, Correll CU, Kane JM. A randomized, double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophr Res.* 2018;195:245-251.

19. Correll CU, Newcomer JW, Silverman B, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: A 24-week phase 3 study. *Am J Psychiatry.* 2020;177(12):1168-1178.

20. Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet.* 1999;37(3):177-193.

21. Turncliff R, DiPetrillo L, Silverman B, Ehrich E. Single- and multiple-dose pharmacokinetics of samidorphan, a novel opioid antagonist, in healthy volunteers. *Clin Ther.* 2015;37(2):338-348.

22. Pathak S, Vince B, Kelsh D, et al. Abuse potential of samidorphan: a phase I, oxycodone-, pentazocine-, naltrexone-, and placebo-controlled study. *J Clin Pharmacol.* 2019;59(2):218-228.

23. Sun L, McDonnell D, Liu J, von Moltke L. Bioequivalence of olanzapine given in combination with samidorphan as a bilayer tablet (ALKS 3831) compared with olanzapine-alone tablets: results from a randomized, crossover relative bioavailability study. *Clin Pharmacol Drug Dev.* 2019;8(4):459-466.
24. Sun L, McDonnell D, Liu J, von Moltke L. Effect of food on the pharmacokinetics of a combination of olanzapine and samidorphan. *Clin Pharmacol Drug Dev.* 2019;8(4):503-510.

25. Sun L, McDonnell D, Yu M, Kumar V, von Moltke L. A phase I open-label study to evaluate the effects of rifampin on the pharmacokinetics of olanzapine and samidorphan administered in combination in healthy human subjects. *Clin Drug Investig.* 2019;39(5):477-484.

26. Sun L, Yagoda S, Du Y, Von Moltke L. Effect of hepatic and renal impairment on the pharmacokinetics of olanzapine and samidorphan given in combination as a bilayer tablet. *Drug Des Devel Ther.* 2019;13:2941-2955.

27. Sun L, Yagoda S, Xue H, et al. Combination of olanzapine and samidorphan has no clinically relevant effects on ECG parameters, including the QTc interval: results from a phase 1 QT/QTc study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2020;100:109881.

28. Sun L, McDonnell D, von Moltke L. Pharmacokinetics and short-term safety of ALKS 3831, a fixed-dose combination of olanzapine and samidorphan, in adult subjects with schizophrenia. *Clin Ther.* 2018;40(11):1845-1854.

29. Kassahun K, Mattiu E, Nyhart E, Jr., et al. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. *Drug Metab Dispos.* 1997;25(1):81-93.

30. Korprasertthaworn P, Polasek TM, Sorich MJ, et al. In vitro characterization of the human liver microsomal kinetics and reaction phenotyping of olanzapine metabolism. *Drug Metab Dispos.* 2015;43(11):1806-1814.

31. Yin A, Shang D, Wen Y, Li L, Zhou T, Lu W. Population pharmacokinetics analysis of olanzapine for Chinese psychotic patients based on clinical therapeutic drug monitoring data with assistance of meta-analysis. *Eur J Clin Pharmacol.* 2016;72(8):933-944.

32. Sun L, Yagoda S, Yao B, Graham C, von Moltke L. Combination of olanzapine and samidorphan has no clinically significant effect on the pharmacokinetics of lithium or valproate. *Clin Drug Investig.* 2020; 40(1):55-64.

33. Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokinet Pharmacodyn.* 2008;35(4):401-421.

34. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.
35. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130(6):461-470.

36. Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug Metab Pharmacokinet.* 2009;24(1):25-36.

37. Lobo ED, Robertson-Plouch C, Quinlan T, Hong Q, Bergstrom RF. Oral olanzapine disposition in adolescents with schizophrenia or bipolar I disorder: a population pharmacokinetic model. *Paediatr Drugs.* 2010;12(3):201-211.

38. Bigos KL, Pollock BG, Coley KC, et al. Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol.* 2008;48(2):157-165.

39. Mauri MC, Paletta S, Di Pace C, et al. Clinical Pharmacokinetics of Atypical Antipsychotics: An Update. *Clin Pharmacokinet.* 2018;57(12):1493-1528.

40. Citrome L, Stauffer VL, Chen L, et al. Olanzapine plasma concentrations after treatment with 10, 20, and 40 mg/d in patients with schizophrenia: an analysis of correlations with efficacy, weight gain, and prolactin concentration. *J Clin Psychopharmacol.* 2009;29(3):278-283.

41. Ortega I, Perez-Ruixo JJ, Stuyckens K, Piotrovsky V, Vermeulen A. Modeling the effectiveness of paliperidone ER and olanzapine in schizophrenia: meta-analysis of 3 randomized, controlled clinical trials. *J Clin Pharmacol.* 2010;50(3):293-310.
FIGURE LEGENDS

Figure 1. Goodness-of-fit and individual weighted residual plots for final population pharmacokinetic models. Observed versus population or individual predicted concentration and individual weighted residual versus individual predicted concentration plots for olanzapine (a) and samidorphan (b).

Figure 2. Prediction-corrected visual predictive check of population pharmacokinetic models for olanzapine (a) and samidorphan (b) over a 24-hour dosing interval. Open circles indicate observed concentrations; the solid line represents the median observed concentration; dashed lines indicate the fifth and 95th percentiles of observed concentrations. The dark blue–shaded region is the 95% prediction interval of the median predicted concentration; the light blue–shaded regions are the fifth and 95th percentiles of predicted concentrations.

Figure 3. Population pharmacokinetic model–predicted covariate effects on steady-state (a) olanzapine $C_{\text{max,ss}}$, (b) olanzapine $AUC_{\text{tau}}$, (c) samidorphan $C_{\text{max,ss}}$, and (D) samidorphan $AUC_{\text{tau}}$.

$^a$Reference $C_{\text{max,ss}}$ for olanzapine is 31.7 ng/mL.

$^b$Reference $AUC_{\text{tau}}$ for olanzapine is 635 ng*h/mL.

$^c$Reference $C_{\text{max,ss}}$ for samidorphan is 33.4 ng/mL.

$^d$Reference $AUC_{\text{tau}}$ for samidorphan is 284 ng*h/mL.

The solid vertical line represents no impact of the covariate using a healthy individual with the following characteristics as a reference subject: age, 36 years; weight, 70 kg; non-black, non-smoking man, with normal hepatic and renal function receiving once-daily oral OLZ/SAM 10 mg/10 mg in a fasted condition. Dashed vertical lines are at 0.8- and 1.25-fold of this value.

$AUC_{\text{tau}}$, area under the plasma concentration-time curve over the daily dosing interval at steady state; $C_{\text{max,ss}}$, maximum concentration at steady state; PI, prediction interval.
Covariate | Statistic or category | Olanzapine | Samidorphan
---|---|---|---
Subjects, n | 601 | 521 | 
Age, years | Median (min–max) | 36 (18–73) | 34 (18–73) |
Sex, n (%) | | | |
| Women | 190 (32) | 151 (29) | 
| Men | 411 (68) | 370 (71) | 
Race, n (%) | | | |
| Native American | 6 (1) | 8 (2) | 

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| Participant type, n (%) | Healthy | With schizophrenia |
|------------------------|---------|-------------------|
| Asian                  | 3 (0)   | 3 (1)             |
| Black                  | 255 (42)| 258 (50)          |
| Hawaiian               | 1 (0)   | –                 |
| Other                  | 7 (1)   | 6 (1)             |
| White                  | 329 (55)| 246 (47)          |

| Body weight, kg         | Median (min–max) |
|-------------------------|------------------|
| Healthy                 | 76.9 (44.0–141.0)| 76.4 (46.5–130.0)|
| With schizophrenia      | 356 (59)         | 226 (43)          |

| Lean body weight, kg    | Median (min–max) |
|-------------------------|------------------|
| Healthy                 | 53.5 (32.0–81.7) | 53.5 (34.2–79.8) |
| With schizophrenia      | 25.5 (17.9–39.2) | 25.6 (17.9–39.1) |

| Body mass index, kg/m²  | Median (min–max) |
|-------------------------|------------------|
| Healthy                 | 4.4 (3.2–5.8)    | 4.4 (3.2–5.8)    |
| With schizophrenia      | 388 (65)         | 404 (78)         |

| ALP, U/L                | Median (min–max) |
|-------------------------|------------------|
| Healthy                 | 71.0 (0.0–167.0) | 69.0 (0.0–167.0) |
| With schizophrenia      | 17.0 (5.0–110.0) | 17.0 (6.0–110.0) |

| ALT, U/L                | Median (min–max) |
|-------------------------|------------------|
| Healthy                 | 18.0 (8.0–244.0) | 18.0 (8.0–244.0) |
| With schizophrenia      | 18.0 (8.0–244.0) | 18.0 (8.0–244.0) |

| Albumin, g/dL           | Median (min–max) |
|-------------------------|------------------|
| Healthy                 | 4.4 (3.2–5.8)    | 4.4 (3.2–5.8)    |
| With schizophrenia      | 388 (65)         | 404 (78)         |

| Creatinine clearance, mL/min | Median (min–max) |
|-----------------------------|------------------|
| Healthy                     | 117 (23.0–260.0) | 117 (23.0–229.0) |
| With schizophrenia          | 104 (20.0–187.0) | 105 (20.0–187.0) |

| Bilirubin, mg/dL            | Median (min–max) |
|-----------------------------|------------------|
| Healthy                     | 0.400 (0.006–2.570) | 0.400 (0.006–2.570) |
| With schizophrenia          | 142 (24)         | 114 (22)         |

| eGFR, mL/min per 1.73 m²    | Median (min–max) |
|-----------------------------|------------------|
| Healthy                     | 117 (23.0–229.0) | 117 (23.0–229.0) |
| With schizophrenia          | 104 (20.0–187.0) | 105 (20.0–187.0) |

| Formulation, n (%)          | Bilayer tablet | Tablet |
|-----------------------------|----------------|--------|
| Healthy                     | 388 (65)       | 213 (35)|
| With schizophrenia          | 142 (24)       | 173 (29)|

| Smoking status, n (%)       | Non-smoker     | Not reported | Smoker |
|-----------------------------|----------------|--------------|--------|
| Healthy                     | 142 (24)       | 173 (29)     | 286 (48)|
| With schizophrenia          | 114 (22)       | 223 (43)     | 184 (35)|

| Hepatic function, n (%)     | Normal         | Mild Impairment | Moderate Impairment | Severe Impairment |
|-----------------------------|----------------|-----------------|---------------------|------------------|
| Healthy                     | 78 (13)        | 10 (2)          | 3 (0)               |                  |
| With schizophrenia          | 454 (76)       | 135 (22)        | 2 (0)               | 10 (2)           |

| Renal function group, eGFR, n (%) | Normal | Mild Impairment | Moderate Impairment | Severe Impairment |
|----------------------------------|--------|-----------------|---------------------|------------------|
| Healthy                          | 454 (76)| 135 (22)       | 2 (0)               | 10 (2)           |
| With schizophrenia               | 408 (78)| 102 (20)       | 1 (0)               | 10 (2)           |

| Renal function group, CRCL, n (%) | Normal | Mild Impairment | Moderate Impairment | Severe Impairment |
|----------------------------------|--------|-----------------|---------------------|------------------|
| Healthy                          | 510 (85)| 64 (12)         | 9 (2)               | 3 (1)            |
| With schizophrenia               | 445 (85)| 102 (20)       | 1 (0)               | 10 (2)           |

| Body mass index category, kg/m², n (%) | ≤25 | >25 |
|----------------------------------------|-----|-----|
| Healthy                                | 277 (46)| 324 (54)|
| With schizophrenia                     | 236 (45)| 285 (55)|

**Parameter** | **Effect** | **Change**
---|---|---
Olanzapine | Inducer effect of rifampin (in the presence vs absence of rifampin) in a | +80%
| Parameter (units) | Estimate | %RSE | 95% CI | CV% |
|------------------|----------|------|--------|-----|
| CL/F (L/h)       | 15.5     | 2.85 | 14.6, 16.4 | –   |
| Vc/F (L)         | 656      | 2.23 | 627, 685  | –   |
| Ka (h⁻¹)         | 0.861    | 5.70 | 0.765, 0.957 | –  |
| ALAG (h)         | 0.782 (fixed) | – | – | – |
| Vp/F (L)         | 225      | 9.42 | 183, 267 | –  |

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| Parameter (units)                                      | Estimate | %RSE | 95% CI      | CV% |
|-------------------------------------------------------|----------|------|-------------|-----|
| CL/F (L/h)                                            | 35.4     | 1.65 | 34.3, 36.5  | –   |
| Vc/F (L)                                              | 297      | 1.63 | 288, 306    | –   |
| Vp/F (L)                                              | 124      | 8.87 | 102, 146    | –   |
| Ka (h⁻¹)                                              | 6.61     | 14.2 | 4.77, 8.45  | –   |
| ALAG (h)                                              | 0.323    | 5.57 | 0.288, 0.358| –   |
| Q/F (L/h)                                             | 12.1     | 7.89 | 10.2, 14.0  | –   |
| WT on CL/F² (fixed)                                   | 0.75     | –    | –           | –   |
| WT on Vc/F² (fixed)                                   | 1.0      | –    | –           | –   |
| Rifampin inducer effect (in the presence vs absence of rifampin) on CL/F | 2.70     | 3.06 | 2.54, 2.86  | –   |
| Moderate hepatic impairment (moderate hepatic impairment vs normal hepatic) on CL/F | 0.810    | 9.04 | 0.667, 0.953| –   |
| Function (severe renal impairment vs normal renal function) on CL/F | 0.570 | 5.96 | 0.503, 0.637 | – |
|---------------------------------------------------------------|-------|------|--------------|---|
| Severe renal impairment (severe renal impairment vs normal renal function) on CL/F | 0.570 | 5.96 | 0.503, 0.637 | – |
| Food (fed vs fasted) on Ka | 0.107 | 36.9 | 0.0296, 0.184 | – |
| Change in ALAG<sup>h.c</sup> | 10.1 | 11.0 | 7.92, 12.3 | – |
| Formulation (samidorphan tablet vs OLZ/SAM bilayer tablet) on ALAG | 1.41 | 5.80 | 1.25, 1.57 | – |
| **Interindividual variability** |     |      |             |   |
| CL/F | 0.087 | 11.9 | 0.066, 0.107 | 29.4 |
| Vc/F | 0.054 | 19.0 | 0.034, 0.075 | 23.3 |
| Ka | 1.76 | 16.8 | 1.18, 2.34 | 219 |
| ALAG | 0.131 | 24.8 | 0.067, 0.195 | 36.2 |
| Vp/F | 0.681 | 24.5 | 0.354, 1.010 | 98.8 |
| Q/F | 0.223 fixed | – | – | 50.0 |
| **Residual variability in σ<sup>2</sup><sub>prop</sub>** | 0.061 | 6.87 | 0.053, 0.069 | 24.7 |