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ARTICLE

Physiologically-Based Pharmacokinetic Modeling for Predicting Drug Interactions of a Combination of Olanzapine and Samidorphan

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A combination of the antipsychotic olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM) is intended to provide the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. As cytochrome P450 (CYP) 1A2 and CYP3A4 are the major enzymes involved in metabolism of olanzapine and samidorphan, respectively, physiologically-based pharmacokinetic (PBPK) modeling was applied to predict any drug-drug interaction (DDI) potential between olanzapine and samidorphan or between OLZ/SAM and CYP3A4/CYP1A2 inhibitors/inducers. A PBPK model for OLZ/SAM was developed and validated by comparing model-simulated data with observed clinical study data. Based on model-based simulations, no DDI between olanzapine and samidorphan is expected when administered as OLZ/SAM. CYP3A4 inhibition is predicted to have a weak effect on samidorphan exposure and negligible effect on olanzapine exposure. CYP3A4 induction is predicted to reduce both samidorphan and olanzapine exposure. CYP1A2 inhibition or induction is predicted to increase or decrease, respectively, olanzapine exposure only.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Cytochrome P450 (CYP)1A2 and CYP3A4 are the major CYP enzymes involved in metabolism of olanzapine and samidorphan, respectively.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What is the potential for drug-drug interactions (DDIs) with CYP3A4 and CYP1A2 modulators when olanzapine and samidorphan are administered in combination as OLZ/SAM?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The physiologically-based pharmacokinetic (PBPK) model predicted changes in exposure for samidorphan and/or olanzapine when OLZ/SAM is administered in the presence of CYP3A4 inhibitors or inducers, CYP1A2 inhibitors, or tobacco smoking.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ In lieu of clinical studies, PBPK modeling can serve as a valuable tool for assessing DDI potential with OLZ/SAM and for supporting regulatory submissions.

Medical and psychiatric comorbidities are common in patients with schizophrenia.[1,2] Management of these comorbid conditions may necessitate the use of additional pharmacologic therapies, exposing patients to a risk of drug-drug interactions (DDIs) between their antipsychotic treatment and concomitant medications.[3] Furthermore, the use of tobacco products also has the potential to alter plasma drug levels and affect the efficacy or safety of psychiatric medications.[4]

Current guidelines for the treatment of schizophrenia endorse the use of antipsychotic medication,[5] and selection of an antipsychotic is generally based on its side effect profile.[6] The atypical antipsychotic olanzapine[7] is considered one of the most effective antipsychotics approved for the treatment of schizophrenia.[8] However, use of olanzapine has been limited by significant weight gain and metabolic effects associated with its use.[9] A combination of olanzapine and samidorphan (OLZ/SAM) is in development to provide the antipsychotic efficacy of olanzapine, while mitigating olanzapine-associated weight gain.

Samidorphan is a new molecular entity that, *in vitro*, binds with high affinity to human μ-opioid, κ-opioid, and δ-opioid receptors, and acts as an antagonist at μ-opioid receptors and partial agonist at κ-opioid and δ-opioid receptors.[10,11] *In vivo*, it has been established that samidorphan functions as an opioid receptor antagonist.[12] In studies enrolling healthy adult subjects[13] and adult patients with schizophrenia,[14] the presence of samidorphan limited olanzapine-induced weight gain in those receiving OLZ/SAM vs. olanzapine alone.

Olanzapine is mainly eliminated via hepatic metabolism, with 7% of the administered dose being excreted renally as unchanged olanzapine.[15,16] The primary metabolic pathways for olanzapine are direct glucuronidation

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via uridine 5'-diphospho-glucuronosyltransferase 1A4 and cytochrome P450 (CYP)-mediated oxidation, mainly by CYP1A2 with minor contributions from CYP2C8, CYP3A4, and CYP2D6.[15,16] Samidorphan is eliminated primarily via CYP3A4-mediated hepatic metabolism and renal excretion.[17,18]

Pharmacokinetic data from clinical studies indicated a lack of DDI between olanzapine and samidorphan when the two drugs are administered in combination,[13,18,19] consistent with their distinct metabolic pathways. The effects of CYP1A2 and CYP3A4 inhibition and induction on the pharmacokinetics of olanzapine and samidorphan have been evaluated in clinical studies (**Table S1**).

Coadministration of olanzapine with fluvoxamine, a strong inhibitor of CYP1A2, increased olanzapine maximum plasma concentration (C_{max}) by 84% and area under the plasma drug concentration-time curve from time 0 to 24 hours (AUC_{0-24}) by 119%.[20] Conversely, clearance of olanzapine increased with agents that induce CYP1A2, including tobacco smoke and carbamazepine.[21–23] Samidorphan C_{max} and AUC from time 0 to infinity (AUC_{∞}) were increased by 12% and 50%, respectively, in the presence of strong CYP3A4 inhibition[24] and decreased by 44% and 73%, respectively, in the presence of a strong CYP3A4 inducer.[25]

Given the effects of CYP1A2 and CYP3A4 modulations on the pharmacokinetics of olanzapine and samidorphan observed in the clinical studies, additional evaluation of the potential for a DDI is warranted to inform on concomitant medication use during OLZ/SAM administration. A physiologically-based pharmacokinetic (PBPK) modeling approach that incorporates a drug's physiochemical properties, human physiological variables, and population variability estimates provides a comprehensive and powerful tool for evaluation of the effects of intrinsic (e.g., age and organ dysfunction) and extrinsic (e.g., DDIs) factors on drug exposures.[26] Where clinical trial data are not available to fully address DDIs, PBPK modeling may allow prospective prediction of DDI potential,[26,27] and it is now considered an acceptable time-saving and resource-saving alternative to clinical studies.[27,28] Therefore, PBPK modeling was used to further examine the DDI potential of OLZ/SAM, using a stepwise, workflow approach.[28]

The objectives of the current analysis were: (i) to develop PBPK models for olanzapine and samidorphan using *in vitro* data and *in vivo* clinical pharmacokinetics data; (ii) to simulate, using those models, the pharmacokinetic profiles of olanzapine and samidorphan after single-dose or multiple-dose administration of each drug alone or in combination as OLZ/SAM; (iii) to verify, using observed data from clinical studies, the model-predicted effect of CYP1A2 and CYP3A4 inhibitors/inducers on the respective pharmacokinetic profiles of olanzapine and samidorphan; and (iv) to use the verified PBPK models to predict the effect of coadministration of OLZ/SAM with CYP3A4 and CYP1A2 modulators (including smoking) on the exposures of olanzapine and samidorphan.

METHODS

Model development

Separate PBPK models were constructed for olanzapine and samidorphan in the Simcyp version 16 Simulator (Certara, Princeton, NJ) and refined by leveraging available *in vitro* data and *in vivo* clinical data. Published physicochemical properties, plasma protein binding, *in vitro* disposition and metabolism profiles of olanzapine obtained from literature searches, and permeability data from an *in vitro* study in the human Caco-2 cell system were used to build a PBPK model for olanzapine (**Table 1**).[15,16,21,29] Physicochemical parameters and parameters from *in vitro* absorption, distribution, metabolism, and excretion studies, and from a clinical mass balance study with samidorphan, were used to build a PBPK model for samidorphan (**Table 1**).

A minimal PBPK model, which includes a single adjusting compartment that combines all tissues except the intestine, liver, and portal vein (**Figure S1a**), was used for olanzapine, and a full PBPK model by inclusion of additional tissues, such as adipose, brain, bone, heart, lung, muscle, and skin (**Figure S1b**) was used for samidorphan, as the selected models described the disposition of each drug with reasonable accuracy when compared with observed clinical data. Application of the full PBPK model for samidorphan led to improved recovery of the observed half-life.

MODEL VALIDATION

The PBPK models were used to simulate concentration-time (C-T) profiles of olanzapine and samidorphan in a virtual North European Caucasian population based on default Simcyp parameter values.[30] Proportions of poor metabolizer phenotypes for relevant CYP enzymes and CYP1A2 abundance values for nonsmokers (52 pmol/mg microsomal protein) and smokers (94 pmol/mg) were obtained from published sources.[30,31]

The PBPK models for olanzapine and samidorphan were first developed and verified using observed data from clinical studies in which olanzapine or samidorphan was administered alone.[13,20] The models were then combined to represent administration of olanzapine and samidorphan in combination as OLZ/SAM in virtual trial simulations to ensure the same virtual individual was administered olanzapine and samidorphan together as in clinical studies with OLZ/SAM.[13,18,19,25] Specifically, the PBPK models were verified by comparing simulated C-T profiles and pharmacokinetic parameters, including C_{max} and AUC, for olanzapine and/or samidorphan with observed data obtained from clinical studies.[13,18–20,24,25] Virtual trials for each comparison were generated to match the population demographics (i.e., age and sex) and treatment characteristics of the study, providing the observed data as described in **Table 2**.

MODEL APPLICATION

The verified OLZ/SAM PBPK model was applied to predict changes in exposure of olanzapine and samidorphan following coadministration of therapeutic doses of orally administered OLZ/SAM with CYP3A4 and CYP1A2 modulators. For each simulation, 10 virtual trials of 24 healthy subjects (50% women; 19–49 years of age) were generated. Change in exposure of olanzapine and samidorphan was predicted after administration of OLZ/SAM 10/10 (10 mg olanzapine and 10 mg samidorphan) or 20/10 (20 mg olanzapine and 10 mg samidorphan): (i) on the last

Table 1 Input parameter values

Parameter		Source/references
Olanzapine		
Molecular weight	**312.43**	http://www.drugbank.ca/drugs/DB00334#admet
log P	**2.89**	El-Ela *et al.*[29]
Compound type	**Monoprotic base**	Callaghan *et al.*[21]
pKa1	**7.24**	Callaghan *et al.*[21]
B:P	**0.62**	Callaghan *et al.*[21]
fu	**0.07**	Kassahun *et al.*[15]
V_{ss} (L/kg)	**5.0**	Optimized[a]
Caco-2 $Papp_{A\text{-}B\ 7.4:7.4}$ (10^{-6} cm/seconds)	**17.37**	Unpublished data provided by Alkermes
Calibrator: atenolol	**0.146**	
$P_{eff,man}$ (10^{-4} cm/seconds)	3.84	Predicted from Caco-2 data
Q_{Gut} (L/hour)	13.8	Predicted from Caco-2 data
Fa	**1.0**	Predicted from Caco-2 data
ka (/hour)	**0.6**	Optimized
$CL_{int,u}$ (µL/minutes/mg)	57.93	Retrograde approach using CL_{PO} from Callaghan *et al.*[21]
CYP1A2	**23.67**	Enzyme contribution based on recombinant data and chemical inhibition data in human liver microsomes; Korprasertthaworn *et al.*[16]
CYP2C8	**4.98**	
CYP3A4	**4.42**	
UGT1A4	**20.58**	
FMO3	**4.28**	
CL_R (L/hour)	**0.81**	Kassahun *et al.*[15]
Samidorphan		
Molecular weight	**370.44**	Unpublished data provided by Alkermes
Log P	**2.4**	Unpublished data provided by Alkermes
Compound type	**Ampholyte**	Unpublished data provided by Alkermes
pKa1 (acid), pKa2 (base)	**7.5; 8.2**	Unpublished data provided by Alkermes
B:P	**1**	Unpublished data provided by Alkermes
fu	**0.69**	Unpublished data provided by Alkermes
V_{ss} (L/kg)	**3.43**	Predicted (Rodgers and Rowland, 2006)[42]
Caco-2 $Papp_{A\text{-}B\ 6.5:7.4}$ (10^{-6} cm/seconds)	**18.77**	Unpublished data provided by Alkermes
Calibrator: atenolol	**0.121**	
$P_{eff,man}$ (10^{-4} cm/seconds)	4.60	Predicted from Caco-2 data
Q_{Gut} (L/hour)	14.8	Predicted from Caco-2 data
Fa	**1.0**	Predicted from Caco-2 data
ka (/hour)	2.01	Predicted from Caco-2 data
	0.7	Optimized
$CL_{int,u}$ (µL/minutes/mg protein)	11.15	Unpublished data provided by Alkermes
CYP3A4	**5.93**	Unpublished data provided by Alkermes
Non-CYP3A4	**5.22**	
CL_R (L/hour)	**11.0**	Unpublished data provided by Alkermes
$K_{i,u}$ (µM): CYP2D6	**41.5**	Unpublished data provided by Alkermes
fu_{mic} at 0.5 mg/mL	**0.86**	

Parameters in bold were used as direct inputs to Simcyp.
B:P, blood-to-plasma partition ratio; $CL_{int,u}$, unbound intrinsic metabolic clearance; CL_{PO}, oral clearance; CL_R, renal clearance; fa, fraction absorbed from the gut; FMO3, flavin-containing monooxygenase 3; fu, fraction unbound in plasma; fu_{mic}, fraction of unbound substrate or inhibitor in a microsomal incubation; ka, first-order absorption rate constant; $K_{i,u}$, enzyme competitive inhibition constant corrected for the fraction of unbound drug; $Papp_{A-B}$, apical-to-basolateral apparent permeability; $P_{eff,man}$, *in vivo* permeability; pKa, negative base-10 logarithm of the acid dissociation constant (Ka) of a solution (ie, $pKa = -\log_{10}Ka$); Q_{Gut}, nominal blood flow in the gut; V_{ss}, volume of distribution at steady-state.
[a]Based on Rodgers and Rowland[42] and Poulin and Thiel.[43]

of 5 days of itraconazole 200 mg/day (a strong CYP3A4 inhibitor); (ii) on the last of 5 days of fluconazole 200 mg/day (after a 400-mg loading dose; a moderate CYP3A4 inhibitor); (iii) on the eighth of 14 days of efavirenz 600 mg/day (a moderate CYP3A4 inducer); and (iv) on the fourth of 8 days of fluvoxamine 100 mg/day (a strong CYP1A2 inhibitor). The effect of smoking, associated with increasing CYP1A2 abundance, was predicted in 10 virtual trials of 12 healthy smokers (CYP1A2 abundance of 94 pmol/mg protein) and 12 healthy nonsmokers (52 pmol P450/mg

Table 2 Population and dosing characteristics of virtual trials used in model validation[a]

Population group (matching observed trial)	Age, years	Sex, % female	Dosing and duration
Healthy subjects, $n = 20$[13]	18–40	0	Once-daily oral olanzapine 10 mg/day and/or samidorphan 5 mg/day (administered alone or in combination) for 21 days
Healthy, nonsmoking subjects, $n = 48$[18]	18–40	41.7	Single oral dose of OLZ/SAM 10 mg/10 mg
Subjects with schizophrenia, $n = 21$ (> 76% smokers)[b,19]	19–53	33.3	7 days of olanzapine lead-in with dose titration up to 15 mg/day followed by once-daily oral OLZ/SAM 10 mg/10 mg for 14 days
Healthy subjects, $n = 24$[24]	19–49	50.0	Single oral dose of samidorphan 2 mg in the absence of and presence of itraconazole (on the last day of 5 days of itraconazole 200 mg/day)
Healthy subjects, $n = 24$[c,25]	20–40	54.2	Single oral dose of OLZ/SAM 10 mg/10 mg in the absence of and presence of rifampin (on the 8th day of 14 days of rifampin 600 mg/day)
Healthy subjects (smokers), $n = 10$[b,20]	18–32	0	Single oral dose of olanzapine 5 mg in the absence of and presence of fluvoxamine (on the fourth day of 9 days fluvoxamine 100 mg/day)

OLZ/SAM, combination of olanzapine and samidorphan.
[a]For each model verification, simulated outputs were based on data from 10 virtual trials.[b]A CYP1A2 abundance of 94 pmol/mg protein was applied.[c]Two sets of simulations were run for the rifampin drug-drug interaction, one using the Simcyp default CYP3A4 induction parameters for rifampin (maximum fold induction [Ind_{max}] = 16; concentration that yields half of the maximum response achievable [Ind_{C50}] = 0.32 μM), and the second using Ind_{C50} = 0.32 μM and the Ind_{max} value derived from mRNA data (29.9-fold).[32]

protein), 19–49 years of age (50% women), receiving a single dose of OLZ/SAM 10/10 or 20/10. The simulations were repeated using a CYP1A2 abundance of 156 pmol P450/mg protein (heavy smokers).

RESULTS

Model validation

Simulated plasma concentrations of olanzapine following multiple oral doses of olanzapine (10 mg) administered alone and in combination with samidorphan (5 mg; **Figure 1a**) were superimposed, as were simulated plasma concentrations of samidorphan following multiple oral doses of samidorphan (5 mg) alone and in combination with olanzapine (10 mg; **Figure 1b**), indicating there is no pharmacokinetic interaction between olanzapine and samidorphan when the two drugs were administered in combination. Simulated plasma concentrations and pharmacokinetic parameters were also in good agreement with observed data[13] (**Figure 1**; **Table S2**). Simulated plasma C-T profiles of olanzapine and samidorphan following a single oral dose of OLZ/SAM in healthy subjects were consistent with observed data[18] (**Figure S2**), as were simulated C-T profiles of olanzapine and samidorphan following multiple once-daily oral doses of OLZ/SAM 10/10 in patients with schizophrenia[19] (**Figure 2**).

Simulated C-T profiles of samidorphan in the absence and presence of the strong CYP3A4 inhibitor itraconazole are consistent with the observed data (**Figure 3**). The model-predicted 58% increase in samidorphan AUC in the presence of itraconazole agrees well with the observed 50% increase after sublingual administration of samidorphan[24] (**Table 3**). Simulated C-T profiles of olanzapine and samidorphan following a single oral dose of OLZ/SAM in the absence and presence of the strong CYP3A4 inducer rifampin are consistent with observed data[25] (**Figure 4**). Using a maximum fold induction (Ind_{max}) value of 29.9 for rifampin,[32] the model predicted 43% and 74% reductions in olanzapine and samidorphan AUC, respectively, in the presence of rifampin, which agreed well with the observed 48% and 73% reductions, respectively (**Table 3**). The model-predicted 92% increase in olanzapine AUC in the presence of the strong CYP1A2 inhibitor fluvoxamine was consistent with the observed increase of 119% (**Table 3**).[20]

MODEL APPLICATION

The validated PBPK model for OLZ/SAM was applied to predict the change in olanzapine and samidorphan exposure following coadministration of OLZ/SAM with itraconazole (a strong CYP3A4 inhibitor), fluconazole (a moderate CYP3A4 inhibitor), and efavirenz (a moderate CYP3A4 inducer). The model predicted a 60% and 39% increase in samidorphan AUC in the presence of the strong CYP3A4 inhibitor itraconazole (200 mg/day) and the moderate CYP3A4 inhibitor fluconazole (200 mg/day), respectively, with minimal change in olanzapine AUC (**Table 3**). The model predicted a 14% reduction in olanzapine AUC and a 41% reduction in samidorphan AUC in the presence of the moderate CYP3A4 inducer efavirenz (600 mg/day) (**Table 3**).

The effects of CYP1A2 inhibition and of smoking, which is associated with induction of CYP1A2, were assessed for olanzapine only, as samidorphan is not metabolized by CYP1A2. The model predicted an increase in olanzapine exposure when OLZ/SAM 10/10 or 20/10 was administered in the presence of the strong CYP1A2 inhibitor fluvoxamine (100 mg/day; **Table 3**). The predicted effect of fluvoxamine coadministration on olanzapine exposure was greater in smokers than in nonsmokers and was independent of olanzapine dose (**Table 3**). A reduction in olanzapine exposure after OLZ/SAM administration was predicted in smokers, assuming CYP1A2 abundance of 94 pmol/mg protein. An even greater reduction in olanzapine exposure was predicted in heavy smokers, assuming a CYP1A2 abundance of 156 pmol/mg protein (**Table 3**).

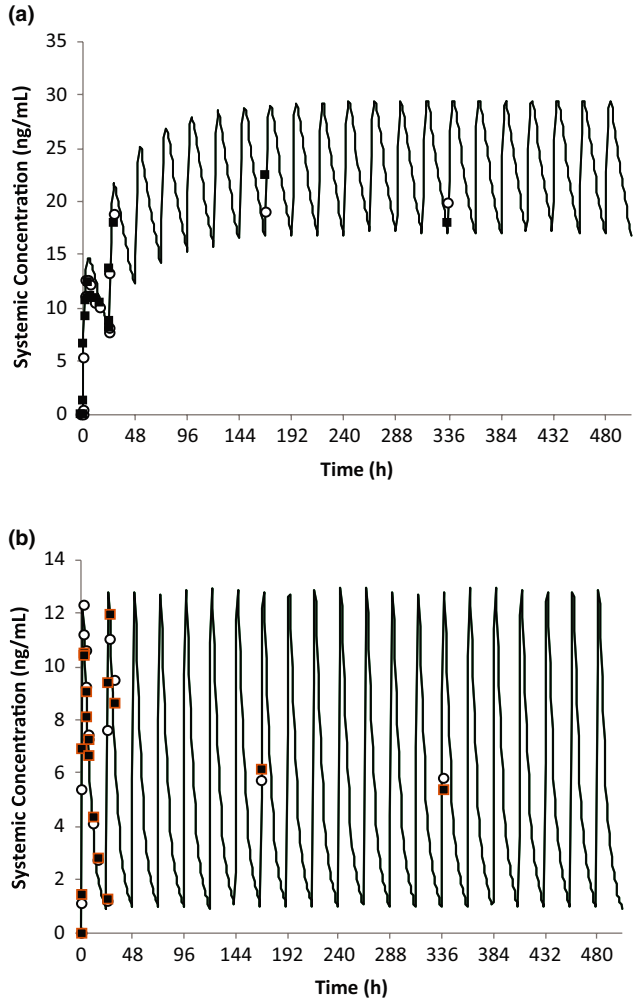

Figure 1 Simulated and observed plasma concentrations of (**a**) olanzapine and (**b**) samidorphan following once-daily oral doses of olanzapine (10 mg) or samidorphan (5 mg) administered alone or in combination. **a** Olanzapine; **b** samidorphan; **a** simulated mean (lines, simulated population; n = 340) and observed (symbols, n = 34)[13] plasma concentrations of olanzapine (10 mg) when olanzapine was administered alone (open circles) or in combination with samidorphan (5 mg) (solid squares). The lines are superimposed (i.e., no interaction is predicted). **b** Simulated mean (lines, simulated population; n = 200) and observed (symbols, n = 20)[13] plasma concentrations of samidorphan (5 mg) when samidorphan was administered alone (open circles) or in combination with olanzapine (10 mg) (solid squares). The lines are superimposed (i.e., no interaction is predicted).

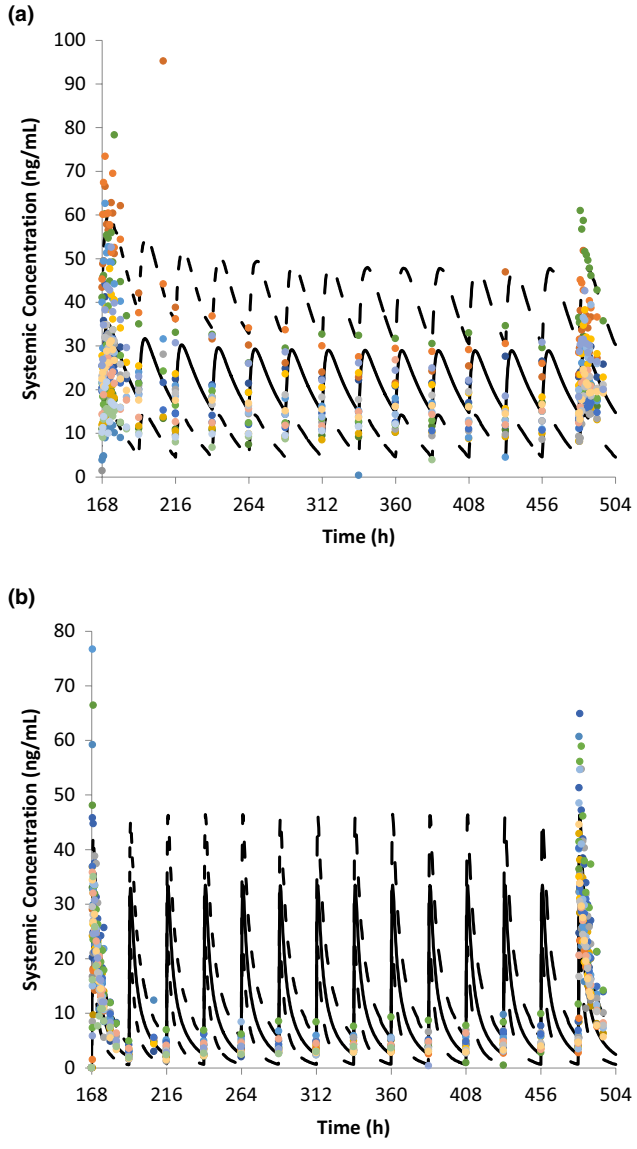

Figure 2 Simulated and observed plasma concentrations of (**a**) olanzapine and (**b**) samidorphan after 7 days of olanzapine lead-in followed by 14 days of once-daily oral doses of combined olanzapine and samidorphan (OLZ/SAM) 10/10 in patients with schizophrenia. **a** Olanzapine; **b** samidorphan; simulated mean (lines, n = 210) and observed individual (symbols, n = 21)[18] plasma concentrations after 7 days of olanzapine lead-in followed by 14 days of once-daily oral doses of OLZ/SAM 10/10 in patients with schizophrenia. The solid line is the mean data for the simulated population, and the dotted lines are the 5th and 95th percentiles. Each color represents one individual patient.

DISCUSSION

Separate PBPK models for olanzapine and samidorphan were developed and verified using observed data from clinical studies in which olanzapine or samidorphan was administered alone.[13,20] First-order models were able to capture the absorption profiles of both olanzapine and samidorphan adequately. Furthermore, given that the change in C_{max} was relatively small (12%) in the clinical study involving samidorphan and the strong CYP3A4 inhibitor itraconazole,[24] first-pass metabolism was not considered a major contributor to DDI liability here.

The two models were combined to represent administration of olanzapine and samidorphan in combination as OLZ/SAM in virtual trial simulations to ensure the same virtual individual with the exact same system/physiological parameters was administered olanzapine and samidorphan together at the same time in the same biosystem as in clinical studies with OLZ/SAM.[13,18,19,25] Model-simulated C-T profiles well described the observed data in multiple clinical studies for model validation. Simulated exposures were

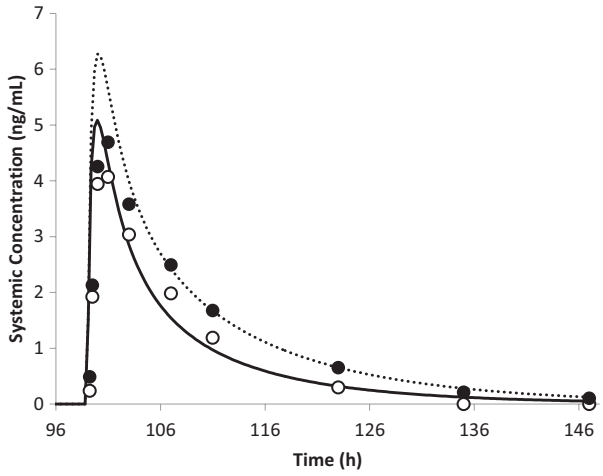

Figure 3 Simulated and observed plasma concentrations of samidorphan following a single oral or sublingual dose of 2 mg samidorphan in the absence and presence of itraconazole. Simulated (lines, *n* = 240) mean plasma concentrations of samidorphan following a single oral dose of 2 mg samidorphan in the absence (solid line) and presence (dotted line) of itraconazole on the fifth day of dosing 200 mg q.d. Displayed for comparison are the observed mean plasma concentrations of samidorphan following a single sublingual dose of BUP/SAM 2/2 (2 mg buprenorphine/2 mg samidorphan) in the absence (open circles) and presence (solid circles) of itraconazole on the fifth day of dosing 200 mg q.d.[24]

within 1.25-fold of observed data for both olanzapine and samidorphan. PBPK modeling predicted no interaction between olanzapine and samidorphan when administered in combination, which is consistent with the distinct metabolic pathways of olanzapine and samidorphan and observed data from clinical studies.[13,18,19]

The weak effect of CYP3A4 inhibition on samidorphan pharmacokinetics was accurately predicted by the PBPK model. The predicted 58% increase in samidorphan AUC in the presence of itraconazole (a strong CYP3A4 inhibitor) aligned well with the 50% increase observed in a clinical DDI study with buprenorphine/samidorphan (BUP/SAM) and itraconazole.[24] Although the observed data were based on sublingual administration of samidorphan as a component of BUP/SAM, because the bioavailability of samidorphan is similar with sublingual and oral administration,[33] the effect of itraconazole on samidorphan pharmacokinetics after oral administration is expected to be the same as that after sublingual administration. The negligible effect of itraconazole on olanzapine exposure predicted by the PBPK model was expected, as the contribution of CYP3A4 to the overall clearance of olanzapine is < 10%,[34,35] and supported by the fact that no significant CYP3A4-mediated DDIs with olanzapine have been reported.[21] Coadministration with a moderate CYP3A4 inhibitor (fluconazole) is predicted to result in a 39% increase in samidorphan AUC and a negligible change in olanzapine exposure.

The reduction in both olanzapine and samidorphan exposure when coadministered with the strong CYP3A4 inducer rifampin was well predicted by PBPK modeling. Although the ratios (presence/absence of rifampin) of C_{max} and AUC values predicted using the default Simcyp Ind_{max} value of 16 for rifampin (olanzapine: 0.88 and 0.72; samidorphan: 0.59 and 0.41, respectively) were generally consistent with observed values (olanzapine: 0.89 and 0.52; samidorphan: 0.56 and 0.27, respectively), published DDI modeling studies have indicated that models perform well with a more potent rifampin induction potential, using maximum fold values of 37.1 and 38.0, respectively.[36,37] An intermediate Ind_{max} value of 29.9, based on mRNA data from an *in vitro* study using human hepatocytes,[32] yielded ratios of C_{max} and AUC values (olanzapine: 0.78 and 0.57; samidorphan: 0.42 and 0.26, respectively) more consistent with observed values compared with the default Ind_{max}. The value of 29.9 has been applied in simulations involving other drugs with CYP3A4 contributions similar to that of samidorphan (including zolpidem and alprazolam). Predicted changes in exposure of both drugs as a consequence of coadministration of rifampin led to good recovery of the observed data in each case (data not shown). Coadministration with a moderate CYP3A4 inducer is predicted to result in a 14% reduction in olanzapine AUC and a 41% reduction in samidorphan AUC.

Inhibition and induction of CYP1A2 are predicted to affect exposure for olanzapine only in individuals receiving OLZ/SAM, as samidorphan is not metabolized by CYP1A2. The OLZ/SAM PBPK model predicted increases of 60% and 102% in olanzapine AUC in nonsmokers and smokers, respectively, when OLZ/SAM was coadministered with a strong CYP1A2 inhibitor. The predicted increase in olanzapine AUC in the presence of strong CYP1A2 inhibition is consistent with that reported in a previous DDI study where coadministration of fluvoxamine (≤ 100 mg/day) with olanzapine (2.5–7.5 mg/day) once daily for 8 days in 10 male smokers resulted in a 119% increase in olanzapine AUC.[20] A smaller 30% to 55% increase in AUC was observed in a second study, in which male smokers (*N* = 10) were administered olanzapine 10 mg in the absence and presence of fluvoxamine 50 or 100 mg/day.[38] When taking OLZ/SAM, smoking is predicted to decrease olanzapine AUC by 23%, assuming a hepatic CYP1A2 abundance of 94 pmol/mg protein in smokers vs. 52 pmol/mg in nonsmokers.[31] Assuming an increase in CYP1A2 abundance to 156 pmol/mg protein in heavy smokers, a 42% decrease in olanzapine AUC is predicted in heavy smokers compared with nonsmokers. Again, this predicted effect is consistent with results obtained for olanzapine administered alone. Clearance of olanzapine was increased 55% in smokers vs. nonsmokers in a population pharmacokinetic analysis (*N* = 523).[39] In a pharmacokinetics study (*N* = 49), AUC for olanzapine was 15% lower in smokers than in nonsmokers, whereas clearance was determined to be 37% to 48% lower in nonsmokers than in smokers.[21] The predicted increase in clearance with smoking is expected, given that smoking is associated with a significantly reduced olanzapine plasma concentration-to-dose ratio in patients with schizophrenia,[40] and case reports suggest that smoking cessation can result in clinically significant changes in symptoms and tolerability requiring dosage reductions of 30% to 40% in patients stabilized on olanzapine.[41]

A PBPK modeling approach can be used to provide information regarding drug pharmacokinetics and predicted

Table 3 Simulated and observed geometric mean ratios for olanzapine and samidorphan C_{max} and AUC

	Olanzapine		Samidorphan	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Model validation				
± Itraconazole (200 mg q.d.)				
Simulated (trial range)			1.25 (1.21–1.29)	1.58 (1.48–1.65)
Observed			1.12	1.50
Simulated/observed			1.12	1.05
± Rifampin (600 mg q.d.)				
Simulated, Ind_{max} = 16[a]	0.88	0.72	0.59	0.41
Simulated, Ind_{max} = 29.9[a]	0.78	0.57	0.42	0.26
Observed	0.89	0.52	0.56	0.27
Simulated/observed, Ind_{max} = 16	0.99	1.38	1.05	1.52
Simulated/observed, Ind_{max} = 29.9	0.88	1.10	0.75	0.96
± Fluvoxamine (100 mg q.d.)				
Simulated (trial range)	1.23 (1.28–1.29)	1.92 (1.74–2.19)		
Observed	1.84	2.19		
Simulated/observed	0.67	0.88		
Model application				
± Itraconazole (200 mg q.d.)				
Simulated (OLZ/SAM 10/10)	1.04	1.07	1.26	1.60
Simulated (OLZ/SAM 20/10)	1.04	1.07		
± Fluconazole				
Simulated (OLZ/SAM 10/10)	1.03	1.06	1.18	1.39
Simulated (OLZ/SAM 20/10)	1.03	1.06		
± Efavirenz				
Simulated (OLZ/SAM 10/10)	0.95	0.86	0.75	0.59
Simulated (OLZ/SAM 20/10)	0.95	0.86		
± Fluvoxamine				
Simulated (OLZ/SAM 10/10)				
Nonsmokers	1.15	1.60		
Smokers	1.26	2.02		
Simulated (OLZ/SAM 20/10)				
Nonsmokers	1.15	1.60		
Smokers	1.26	2.02		
Smokers vs. nonsmoker[b]				
10 mg olanzapine (OLZ/SAM 10/10)				
CYP1A2: 94 pmol/mg protein	0.91	0.77		
CYP1A2: 156 pmol/mg protein	0.81	0.58		
20 mg olanzapine (OLZ/SAM 20/10)				
CYP1A2: 94 pmol/mg protein	0.91	0.77		
CYP1A2: 156 pmol/mg protein	0.81	0.58		

AUC, area under the plasma drug concentration-time curve; C_{max}, maximum plasma concentration; Ind_{max}, maximum fold induction; OLZ/SAM, combination of olanzapine and samidorphan.

[a]Ind_{max} values of 16 and 29.9 were based on drug-drug interaction predictions involving data from clinical studies of rifampin or from *in vitro* studies of human donor hepatocytes, respectively.[32b]Predicted geometric mean ratios for C_{max} and AUC in smokers relative to nonsmokers following a single oral dose of OLZ/SAM 10/10 or 20/10; simulations were repeated using CYP1A2 abundance values of 94 and 156 pmol/mg protein.

effects of intrinsic and extrinsic factors on absorption, distribution, metabolism, and excretion.[26] Model predictions may be valuable for examining potential differences in pharmacokinetics between patient populations and effects of organ impairment, selecting appropriate dosing regimens for clinical trials, and understanding the potential for DDIs where clinical data are sparse.[26] Possible effects of DDIs can be difficult to predict, particularly for drugs that are susceptible to both induction and inhibition. For OLZ/SAM, each of the two component drugs is known to be subject to DDIs via one or more enzyme pathways when administered alone,[20–22,25] but clinical data assessing DDI potential of OLZ/SAM are currently limited to a single study.[25] In this analysis, PBPK modeling was used to elucidate DDI potential for olanzapine and samidorphan when administered as OLZ/SAM in lieu of clinical studies.

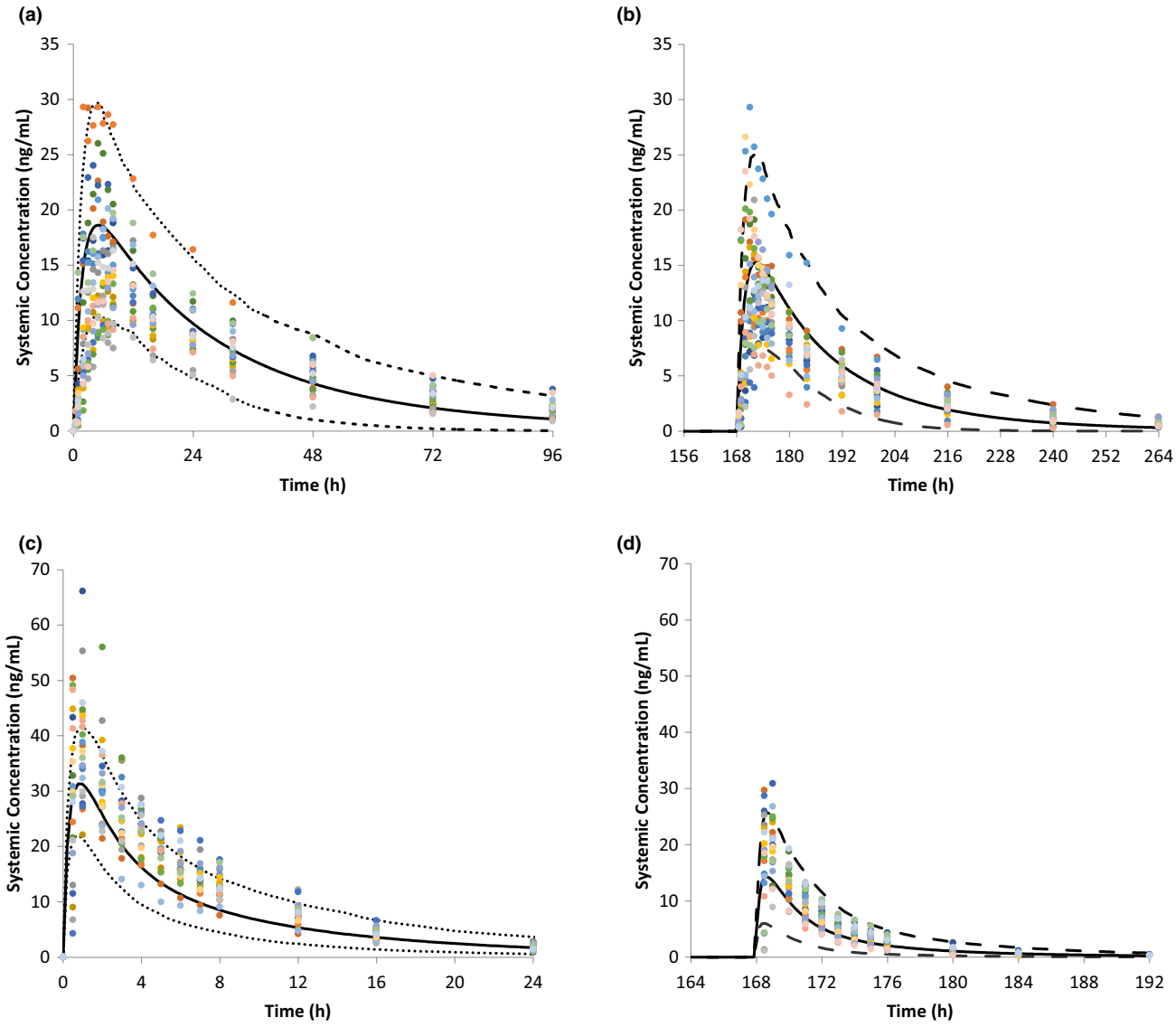

Figure 4 Simulated and observed plasma concentrations of olanzapine and samidorphan following a single oral dose of OLZ/SAM 10/10 in the absence and presence of rifampin. (**a**) Olanzapine in absence of rifampin; (**b**) olanzapine in presence of rifampin; (**c**) samidorphan in absence of rifampin; (**d**) samidorphan in presence of rifampin; simulated (lines, $n = 240$) and observed (circles, $n = 24$)[25] plasma concentrations following a single oral dose of OLZ/SAM 10/10 in the absence and presence of rifampin, assuming an maximum fold induction (Ind_{max}) of 29.9 for rifampin. The solid line is the mean data for the simulated population; dotted lines are the 5th and 95th percentiles.

CONCLUSIONS

The validated OLZ/SAM PBPK model serves as a valuable tool for elucidating the potential for DDIs with coadministration of OLZ/SAM and CYP3A4 or CYP1A2 modulators in lieu of clinical studies. PBPK modeling indicated no pharmacokinetic interaction between olanzapine and samidorphan when administered in combination as OLZ/SAM. Strong inhibition of CYP1A2 is predicted to increase exposure of olanzapine, and induction of CYP1A2 (associated with smoking) is predicted to reduce exposure of olanzapine. Coadministration with moderate and potent CYP3A4 inhibitors is predicted to have a weak effect on samidorphan exposure and negligible effect on olanzapine exposure. Moderate to strong CYP3A4 inducers are predicted to reduce samidorphan exposure and, to a lesser extent, olanzapine exposure.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Supplemental Information. Tables S1-S2. Figures S1-S2.

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Conflicts of Interest. L.S. and L.vM. are employees of Alkermes, Inc. K.R.Y. is an employee of Certara UK Limited, Simcyp Division.

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