Olanzapine and Samidorphan in Pediatric Patients With Bipolar I Disorder: Pharmacokinetic Results From a Phase 1, Multidose, Open-Label Study

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BACKGROUND

- A combination of olanzapine and samidorphan (OLZ/SAM) is approved for the treatment of adults with schizophrenia or bipolar I disorder (BD-I)[1] and is being assessed in a phase 3 clinical trial in pediatric patients
- In a previous pharmacokinetic study of OLZ/SAM in adults with schizophrenia, olanzapine exposure increased dose proportionally while samidorphan exposure was consistent between olanzapine doses[2]
- In pediatric patients (10–12 years old), however, the pharmacokinetic properties of OLZ/SAM may be different than those observed in adults

OBJECTIVE

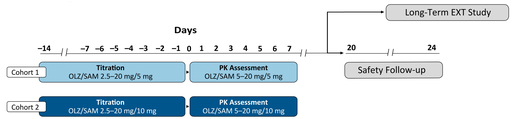
- To evaluate the pharmacokinetic profile of OLZ/SAM in pediatric patients with BD-I

METHODS

Study Design and Patients

- This was a phase 1, multicenter, open-label study (NCT04987658) evaluating the pharmacokinetic profile of OLZ/SAM in clinically stable pediatric patients with BD-I
- Patients aged 10 to 12 years with BD-I as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition,[3] were eligible
- Patients were assigned to 1 of 2 cohorts receiving OLZ/SAM with samidorphan 5 mg (cohort 1) or 10 mg (cohort 2) of (**Figure 1**)
- Patients then underwent a 14-day olanzapine titration of OLZ/SAM to a target dose of 10 mg, with a maximum of 20 mg
- After titration, once-daily OLZ/SAM was administered orally for 7 days to the following groups:
  - OLZ/SAM 5–20 mg/5 mg
  - OLZ/SAM 5–20 mg/10 mg
- On day 7, blood was collected ≤1 hour predose and at 1, 2, 4, 7, and 24 hours postdose
- At the end of the study, patients had the option of enrolling in an open-label extension safety study or resuming their previous standard of care and participating in a follow-up safety visit

Figure 1. Study Design



EXT, extension; OLZ/SAM, combination olanzapine and samidorphan; PK, pharmacokinetic.

Assessments

- Maximum concentration (C_{max}) and areas under the concentration-time curve over the past 24-hour dosing interval (AUC_{0-24h}) and last measurable concentration (AUC_{last}) were calculated for olanzapine and samidorphan
  - Because few patients were assigned to each olanzapine dose and olanzapine and samidorphan do not have any drug-drug interactions,[a] olanzapine data were pooled between cohorts
- Adverse event (AE) incidences were evaluated
- Exploratory assessments included change from baseline on the Clinical Global Impressions–Bipolar scale (CGI-BP), Children's Depression Rating Scale–Revised (CDRS-R), and Young Mania Rating Scale (YMRS)

RESULTS

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	OLZ/SAM 5–20 mg/5 mg (n=3)	OLZ/SAM 5–20 mg/10 mg (n=4)	All Patients (N=7)
Age, mean (SD), years	10.7 (0.6)	11.3 (0.5)	11.0 (0.6)
Male, n (%)	2 (66.7)	2 (50.0)	4 (57.1)
Race,[a] n (%)			
White	2 (66.7)	1 (25.0)	3 (42.9)
Black or African American	1 (33.3)	3 (75.0)	4 (57.1)
Weight , mean (SD), kg	56.0 (3.6)	49.7 (5.4)	52.4 (5.5)
BMI, mean (SD), kg/m^2	26.6 (1.7)	21.0 (1.8)	23.4 (3.4)
CDRS-R score,[b] mean (SD)	25.3 (4.9)	33.8 (9.9)	30.1 (8.8)
CGI-BP score,[c] mean (SD)	9.0 (2.0)	10.3 (2.6)	9.7 (2.3)
YMRS score,[d] mean (SD)	24.0 (28.8)	31.5 (19.8)	28.3 (22.1)

[a]No Asian or Hispanic patients were enrolled. [b]Higher scores indicate greater depression severity. [c]Higher scores indicate greater illness severity. [d]Scores ≥25 correspond to "severely ill."
BMI, body mass index; CDRS-R, Children's Depression Rating Scale–Revised; CGI-BP, Clinical Global Impressions–Bipolar; OLZ/SAM, combination olanzapine and samidorphan; YMRS, Young Mania Rating Scale.

Samidorphan and olanzapine exposures in pediatric patients with bipolar I disorder

Figure 2. Plasma Concentrations of Samidorphan

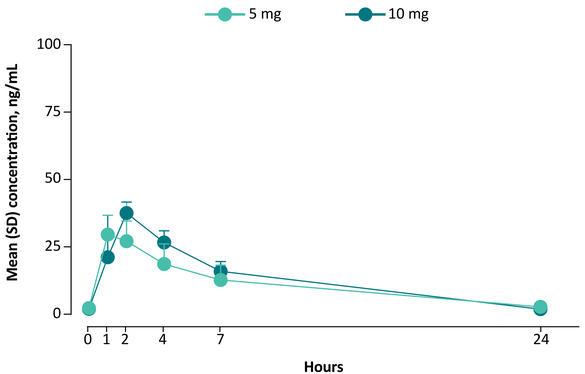


Table 2. Pharmacokinetic Parameters of Samidorphan[a]

Parameters	Samidorphan 5 mg (n=3)	Samidorphan 10 mg (n=4)
C_{max}, geometric mean (CV%), ng/mL	31.5 (11.3)	37.4 (11.0)
AUC_{0-24h}, geometric mean (CV%), ng·h/mL	243.6 (38.4)	315.4 (16.3)
AUC_{last}, geometric mean (CV%), ng·h/mL	240.5 (40.5)	315.2 (16.4)

[a]In adults with schizophrenia, geometric mean C_{max} was 41.7 ng/mL and geometric mean AUC_{0-24h} was 349 ng·h/mL for samidorphan after 14 days of exposure to OLZ/SAM (10/10 mg).[2]

AUC_{0-24h}, area under the concentration-time curve over the 24-hour dosing interval; AUC_{last}, area under the concentration-time curve calculated using the trapezoidal method from time zero to the time of the last quantifiable concentration; C_{max}, maximum concentration observed; CV, coefficient of variation.

Exploratory Efficacy

- Mean (SD) changes from baseline to day 8 in exploratory assessments of clinical symptoms for the OLZ/SAM 5–20 mg/5 mg cohort and the OLZ/SAM 5–20 mg/10 mg cohort were:
  - –3.0 (4.4) and –2.3 (8.7), respectively, for the CDRS-R
  - –2.7 (3.1) and –2.3 (2.5), respectively, for the CGI-BP
  - –19.3 (28.5) and –12.0 (13.6), respectively, for the YMRS

Figure 3. Plasma Concentrations of Olanzapine

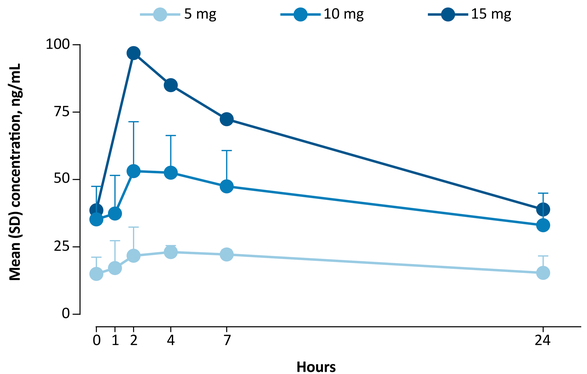


Table 3. Pharmacokinetic Parameters of Olanzapine[a,b]

Parameters	Olanzapine 5 mg (n=3)	Olanzapine 10 mg (n=3)	Olanzapine 15 mg (n=1)
C_{max}, geometric mean (CV%), ng/mL	25.2 (27.6)	53.5 (28.3)	96.9 (NC)
AUC_{0-24h}, geometric mean (CV%), ng·h/mL	477.4 (28.4)	1059.0 (29.0)	1504.8 (NC)
AUC_{last}, geometric mean (CV%), ng·h/mL	464.2 (21.3)	890.0 (13.8)	1531.1 (NC)

[a]No patient received olanzapine 20 mg. [b]In adults with schizophrenia, geometric mean C_{max} was 30.1 ng/mL and geometric mean AUC_{0-24h} was 503 ng·h/mL for olanzapine after 14 days of exposure to OLZ/SAM (10/10 mg).[2]

AUC_{0-24h}, area under the concentration-time curve over the 24-hour dosing interval; AUC_{last}, area under the concentration-time curve calculated using the trapezoidal method from time zero to the time of the last quantifiable concentration; C_{max}, maximum concentration observed; CV, coefficient of variation; NC, not calculated.

LIMITATIONS

- Only 7 pediatric patients with BD-I, all of whom were in a narrow age range (10–12 years old), were enrolled
- Body mass index was not balanced across groups
- Data comparing pediatric patients with BD-I to adults with schizophrenia should be interpreted with caution
- Changes from baseline in exploratory assessments of clinical symptoms, such as the YMRS, should be interpreted with caution due to the small number of patients, the short duration of treatment, and the lack of a control cohort

Table 4. Summary of Adverse Events

Categories[a]	OLZ/SAM 5–20 mg/5 mg (n=3)	OLZ/SAM 5–20 mg/10 mg (n=4)	All Patients (N=7)
Any AE, n (%)	3 (100)	2 (50.0)	5 (71.4)
AEs by highest severity, n (%)			
Mild	2 (66.7)	2 (50.0)	4 (57.1)
Moderate	1 (33.3)	0	1 (14.3)
Severe	0	0	0
AEs leading to discontinuation, n (%)	0	0	0
Any drug-related AE, n (%)	3 (100)	1 (25.0)	4 (57.1)
Any SAE, n (%)	0	0	0
Most common AEs in ≥1 patient, n (%)			
Diarrhea	2 (66.7)	0	2 (28.6)
Fatigue	1 (33.3)	1 (25.0)	2 (28.6)
Headache	2 (66.7)	0	2 (28.6)
Weight increased	2 (66.7)	0	2 (28.6)

[a]Any patient who experienced ≥1 AE in a category was counted only once in that category.
AE, adverse event; OLZ/SAM, combination olanzapine and samidorphan; SAE, serious adverse event.

CONCLUSIONS

- In this study of OLZ/SAM in clinically stable pediatric patients with BD-I:
  - Samidorphan exposures increased with increase in dose from 5 to 10 mg
  - Samidorphan exposures at 10 mg were comparable with those observed in previous studies of adults with schizophrenia[2]
  - Olanzapine exposures increased dose proportionally from 5 to 15 mg
  - Consistent with the olanzapine label, olanzapine exposure in pediatric patients was higher than that in adults, likely due to lower average body weight[4]
- AEs were mild or moderate in severity
- Exploratory assessment results suggest a reduction in clinical symptoms of BD-I during the study
- These data support the use of 10 mg of samidorphan for 10- to 12-year-old patients in the ongoing phase 3 pediatric studies of OLZ/SAM

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AUTHOR DISCLOSURES AND ACKNOWLEDGMENTS

Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

MD has received research support from Alkermes, Allergan, Janssen, Johnson & Johnson, Lundbeck, Myriad, the National Institute of Mental Health, Otsuka, the Patient-Centered Outcomes Research Institute, Pfizer, Shire, and Sunovion; and has been a consultant for, advisory board member of, or received honoraria from Alkermes, Johnson & Johnson, Medscape, Myriad, Sage, and Xenon. **LZ, IL,** and **LF** are or were employees of Alkermes, Inc., and may own stock/options in the company. **DM** is or was an employee of Alkermes Pharma Ireland Ltd. and may own stock/options in the company.

Supported by funding from Alkermes, Inc.