Long-Term Safety and Efficacy of Olanzapine/Samidorphan in a Subgroup of Early-in-Illness Patients

Jacob S. Ballon, MD, MPH,[1] Christina Arevalo, MS,[2] Shifang Liu, PhD,[2] Christoph U. Correll, MD[3-7]

[1]Stanford University, Department of Psychiatry, Stanford, CA, USA; [2]Alkermes, Inc., Waltham, MA, USA; [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA; [4]Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany; [5]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA; [6]Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Northwell Health, New Hyde Park, NY, USA; [7]German Center for Mental Health (DZPG), partner site Berlin, Germany

BACKGROUND

- Olanzapine-associated weight gain and metabolic risk are important concerns when treating patients with schizophrenia or bipolar I disorder (BD-I) who are early in their illness[1]
- Combined olanzapine and samidorphan (OLZ/SAM) is approved in the United States for the treatment of adults with schizophrenia or BD-I[2]
- ENLIGHTEN-Early was a phase 3 clinical trial that evaluated OLZ/SAM in early-in-illness patients
  - After 12 weeks of treatment, OLZ/SAM resulted in less weight gain than olanzapine while providing similar antipsychotic efficacy[3]
- Patients who completed ENLIGHTEN-Early were eligible to enroll in a long-term open-label extension study
  - In the overall study cohort, treatment with OLZ/SAM maintained symptom control and was associated with small changes in body weight and minimal changes in waist circumference in patients with schizophrenia, schizophreniform disorder, or BD-I[4]
  - To date, long-term outcomes in patients who started OLZ/SAM early in their illness have not been evaluated separately from the overall cohort
- This post hoc analysis focused on early-in-illness patients with schizophrenia, schizophreniform disorder, or BD-I who entered the long-term open-label extension study after completing ENLIGHTEN-Early

OBJECTIVE

- To analyze the safety, tolerability, and durability of treatment effect of OLZ/SAM in early-in-illness patients who enrolled in a long-term open-label extension study of adults with schizophrenia, schizophreniform disorder, or BD-I

METHODS

- This study was a post hoc analysis of NCT03201757, a phase 3, 2- to 4-year, multicenter, open-label extension study assessing the safety, tolerability, and durability of treatment effect of OLZ/SAM[2]
- The antecedent ENLIGHTEN-Early trial (NCT03187769) enrolled early-in-illness patients aged 16–39 years who were within 4 years of symptom onset and had <24 weeks of cumulative lifetime antipsychotic exposure[4]
- Patients were eligible to enroll in the long-term open-label extension study within 7 days of completing 1 of 2 open-label studies of 52 weeks or ENLIGHTEN-Early (**Figure 1**) and could receive up to 4 additional years of OLZ/SAM treatment (olanzapine 5–20 mg + samidorphan 10 mg)[4]
  - The current analysis focused on patients enrolling in the long-term open-label extension study from ENLIGHTEN-Early
- Safety assessments included incidences of adverse events (AEs) and changes from baseline in body weight, waist circumference, and lipid (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides) and glycemic (glycosylated hemoglobin [HbA_{1c}] and glucose) parameters
- Durability of treatment effect was assessed with the Clinical Global Impression–Severity (CGI-S) scale
- To illustrate the distribution and variability of body weight and waist circumference changes over time, box-and-whisker plots displaying medians, interquartile ranges, and upper and lower whisker values were generated in 6-month intervals
- Changes from baseline in lipid and glycemic parameters and CGI-S score were summarized in 6-month intervals with means and SEs

Figure 1. Study Design

BD-I, bipolar I disorder; EXT, extension; OLZ/SAM, combination olanzapine and samidorphan.

RESULTS

- Overall, 251 early-in-illness patients were enrolled in the long-term open-label extension study, and 250 of them received ≥1 dose of OLZ/SAM
  - 74/250 (29.6%) and 31/250 (12.4%) received 2 or 3 years of treatment, respectively
  - Few patients (n=12) provided 4-year data; as a result, while all patients had the opportunity to receive at least 2 years of additional OLZ/SAM treatment, not all patients could complete 4 years of follow-up
- Outcomes in the early-in-illness cohort were generally consistent with those from the full cohort in the long-term open-label extension study
  - OLZ/SAM treatment was associated with small changes from baseline in body weight and minimal changes in waist circumference (**Figure 2**) at 2 and 3 years
- Mean CGI-S scores remained stable over 3 years (**Figure 3**)
- Mean changes from baseline in total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides (**Figure 4**), HbA_{1c}, and glucose (**Figure 5**) were minimal
- The safety profile of OLZ/SAM in early-in-illness patients was generally consistent with that in the full cohort in the long-term open-label extension study
  - Overall, 66.4% of patients reported an AE (**Table 2**), and most were mild or moderate in severity
  - AEs leading to treatment discontinuation were rare (14/250 [5.6%])

RESULTS

Figure 2. Changes From Baseline in Body Weight and Waist Circumference[a]

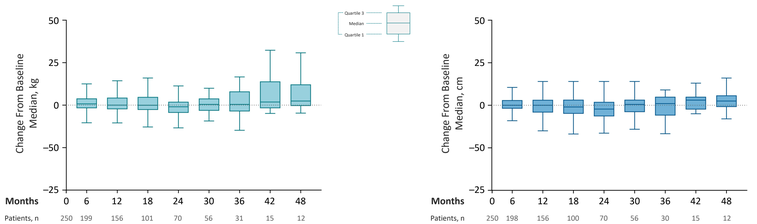


Figure 3. Changes From Baseline in CGI-S Score[a]

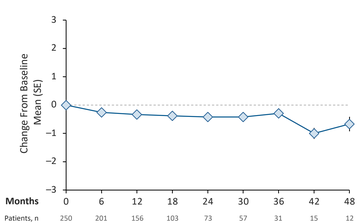


Figure 4. Changes From Baseline in Lipid Parameters[a]

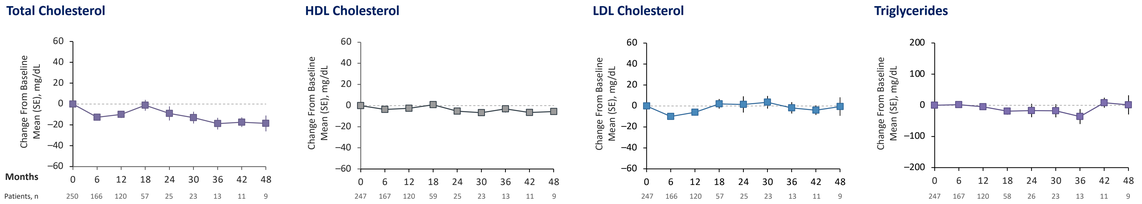
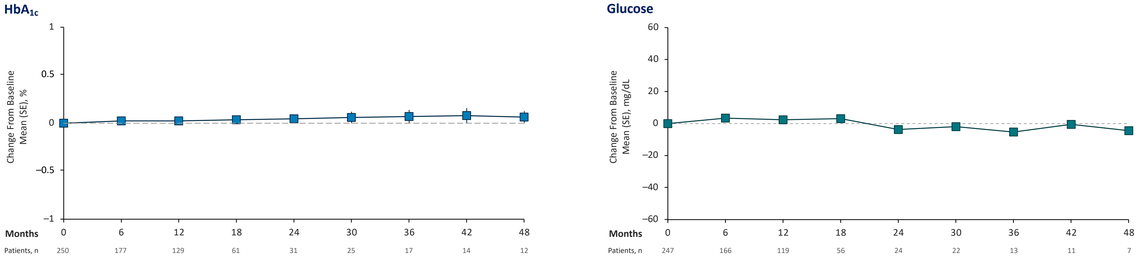


Figure 5. Changes From Baseline in Glycemic Parameters[a]



[a]Few patients (n=12) provided 4-year data.
CGI-S, Clinical Global Impression–Severity; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 1. Baseline Characteristics of Early-in-Illness Patients Enrolled in the Long-Term Open-Label Extension Study

Characteristics	All Patients (N=250)[a]
Age, mean (SD), years	26.4 (6.3)
Sex, n (%)	
Male	164 (65.6)
Female	86 (34.4)
Race, n (%)	
White	203 (81.2)
Black or African American	38 (15.2)
Asian	5 (2.0)
Other/multiple[b]	4 (1.6)
Region, n (%)	
US	74 (29.6)
Non-US	176 (70.4)
Weight, mean (SD), kg	75.5 (13.7)
BMI, mean (SD), kg/m²	25.1 (3.7)
CGI-S score, mean (SD)	3.2 (1.0)

[a]All early-in-illness patients in the long-term open-label extension study who received ≥1 dose of OLZ/SAM. [b]"Other" includes patients who were American Indian or Alaska Native individuals, those reporting multiple races, and those responding "other."
BMI, body mass index; CGI-S, Clinical Global Impression–Severity.

Table 2. Summary of Adverse Events in Early-in-Illness Patients Enrolled in the Long-Term Open-Label Extension Study

Categories[a]	All Patients (N=250)[b]
Any AE, n (%)	166 (66.4)
AEs by highest severity, n (%)	
Mild	82 (32.8)
Moderate	70 (28.0)
Severe	14 (5.6)
AEs leading to discontinuation	14 (5.6)
Any SAE	19 (7.6)
SAEs leading to death[c]	1 (0.4)
Most common AEs (≥5% of patients)	
Weight increased	28 (11.2)
Somnolence	27 (10.8)
Nausea	24 (9.6)
Anxiety	23 (9.2)
Headache	22 (8.8)
Insomnia	22 (8.8)
Blood creatine phosphokinase increased	13 (5.2)

[a]Patients who experienced >1 AE in a category were counted only once in that category. [b]All early-in-illness patients in the long-term open-label extension study who received ≥1 dose of OLZ/SAM. [c]One SAE resulted in death during the study (completed suicide); the investigator assessed this event as not related to study treatment.
AE, adverse event; SAE, serious adverse event.

LIMITATIONS

- The lack of a comparator arm may limit interpretation of safety and efficacy data
- Missing data due to patients who discontinued may have affected the results; patients with a less favorable outcome may have dropped out of ENLIGHTEN-Early or the long-term open-label extension study, creating potential selection bias
- Sample sizes after year 3 were low; although 12 patients completed 4 years of treatment, outcome-specific sample sizes were small because not all patients had available data
- Fasting status was based solely on self-report and not confirmed
- Patients with schizophreniform disorder were enrolled in the long-term open-label extension study but not included in these analyses due to small sample sizes

CONCLUSIONS

- In this post hoc analysis of early-in-illness patients, OLZ/SAM was associated with small changes in body weight, minimal changes in waist circumference, and minimal changes in lipid and glycemic parameters
- Efficacy and safety outcomes were generally consistent with results from the full long-term open-label extension study
- Long-term outcomes with up to 3 years of OLZ/SAM treatment support its safety and clinical effectiveness as maintenance therapy for early-in-illness patients with schizophrenia or BD-I

REFERENCES

1. Correll CU, et al. *JAMA Psychiatry*. 2014;71:1350-1363. DOI: 10.1001/jamapsychiatry.2014.1314. **2.** Lybalvi [package insert]. Waltham, MA: Alkermes, Inc.; 2025. **3.** Kahn RS, et al. *J Clin Psychiatry*. 2023;84:22m14674. DOI: 10.4088/JCP.22m14674. **4.** Ballon JS, et al. *J Clin Psychiatry*. 2025;86(1):24m15511. DOI: 10.4088/JCP.24m15511.

Supported by funding from Alkermes, Inc.

Long-Term Safety and Efficacy of Olanzapine/Samidorphan in a Subgroup of Early-in-Illness Patients

Jacob S. Ballon, MD, MPH,[1] Christina Arevalo, MS,[2] Shifang Liu, PhD,[2] Christoph U. Correll, MD[3-7]

[1]Stanford University, Department of Psychiatry, Stanford, CA, USA; [2]Alkermes, Inc., Waltham, MA, USA; [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA; [4]Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany; [5]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA; [6]Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Northwell Health, New Hyde Park, NY, USA; [7]German Center for Mental Health (DZPG), partner site Berlin, Germany

ACKNOWLEDGMENTS

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

DISCLOSURES

JSB has been a consultant and/or advisor for Alkermes, Aluco BioSciences, Corcept, Indivior, Lundbeck, and Teva; has received grant support from Alkermes, Boehringer Ingelheim, Bristol Myers Squibb (Karuna Therapeutics), Corcept, Janssen, Neurocrine, Roche, and Teva; holds stock options from Aluco BioSciences; and has received royalties from American Psychiatric Association Publishing.

CA and SL are or were employees of Alkermes, Inc., and may own stock/options in the company.

CUC has been a consultant and/or advisor for or has received honoraria from AbbVie, Alkermes, Allergan, Angelini, Aristo, Autobahn, Boehringer Ingelheim, Bristol Myers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Draig, Eli Lilly, EuMentis Therapeutics, Gedeon Richter, GH Research, Hikma, Holmusk, Intra-Cellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedinCell, MedLink Global, Merck, MindPax, Mitsubishi Tanabe Pharmaceuticals, MapLight, Mylan, Neumora Therapeutics, Neuraxpharm, Neurocrine, Neurelis, Neurosterix, NeuShen, Neusignal Therapeutics, Newron, Noven, Novo Nordisk, Orion Pharma, Otsuka, PPD Biotech, Recognify Life Science, Recordati, Relmada, Response Pharmaceutical, Reviva, Rovi, Saladax, Sanofi, Seqirus, Servier, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris, and Xenon Pharmaceuticals; provided expert testimony for Janssen, Lundbeck, Neurocrine, and Otsuka; served on a data safety monitoring board for Compass Pathways, Intra-Cellular Therapies, Relmada, Reviva, and Rovi; received grant support from Boehringer Ingelheim, Janssen, and Takeda; received royalties from UpToDate; and is also a stock option or stock holder of Cardio Diagnostics, Kūleon Biosciences, LB Pharmaceuticals, MedLink Global, MindPax, Quantic, and Terran.

Supported by funding from Alkermes, Inc.