Long-Term Safety and Efficacy of Olanzapine and Samidorphan: Results of a 4-Year Open-Label Study

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BACKGROUND

- Olanzapine is an effective antipsychotic medication for the treatment of schizophrenia and bipolar I disorder (BD-I), but its clinical use is limited by weight gain and metabolic concerns[1-4]
- Olanzapine combined with samidorphan (OLZ/SAM) is approved for the treatment of schizophrenia and BD-I in adults[5]
- OLZ/SAM provides the established antipsychotic efficacy of olanzapine but with less weight gain[6-8]

OBJECTIVE

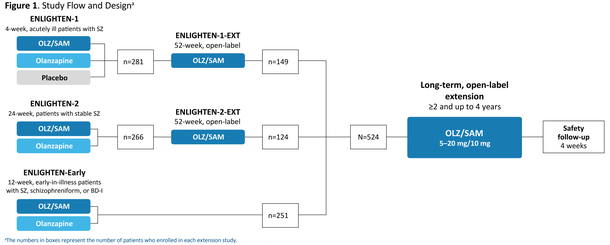
- Evaluate the long-term safety, tolerability, and durability of therapeutic effect of OLZ/SAM in patients with up to 4 years of open-label treatment experience

METHODS

Study Design and Treatments

- This was a phase 3, 4-year (48-month), multicenter, open-label extension study (NCT03201757)
- Eligible patients were enrolled within 7 days of completing 1 of 3 previously conducted phase 3 clinical trials investigating OLZ/SAM (**Figure 1**)
  - Two separate 52-week, open-label extension studies that enrolled patients who completed a pivotal phase 3 randomized controlled trial in adults with schizophrenia
  - A 12-week randomized controlled trial that compared the efficacy and safety/tolerability of OLZ/SAM with that of olanzapine in young adults with recent-onset schizophrenia, schizophreniform disorder, or BD-I
- Prior OLZ/SAM exposure ranged from 0 to 76 weeks of therapy in those studies

Figure 1. Study Flow and Design[a]



[a]The numbers in boxes represent the number of patients who enrolled in each extension study.
BD-I, bipolar I disorder; EXT, extension; OLZ/SAM, olanzapine combined with samidorphan; SZ, schizophrenia.

- All enrolled patients met eligibility criteria for the antecedent study at the time of enrollment in that study
- Patients continued the same daily dose of OLZ/SAM (olanzapine 5–20 mg + samidorphan 10 mg) or the OLZ/SAM equivalent of the olanzapine dose received in their antecedent study for at least 2 and up to an additional 4 years; dose adjustments were determined by the investigator

Assessments

- Key efficacy outcome
  - Clinical Global Impressions–Severity (CGI-S) scale (observed cases)
- Key safety outcomes
  - Changes from baseline (observed cases) in
    - Body weight
    - Waist circumference
    - Lipid (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride) and glycemic (glucose and glycosylated hemoglobin) parameters
  - Incidence and severity of adverse events (AEs)

RESULTS

Patient Disposition and Baseline Characteristics

- Of 524 patients enrolled, 523 received ≥1 dose of OLZ/SAM (**Table 1**)
- Because of patient discontinuations that occurred due to the Ukraine-Russia conflict (n=72), only 451 patients were eligible to receive at least 2 years of open-label OLZ/SAM treatment; of those, 242 (53.7%) completed 2 years of treatment
- 335 patients were eligible to receive up to 4 years of treatment after the protocol was modified from a 2- to a 4-year treatment period, with 109 (32.5%) completing 4 years
- Mean (SD) duration of exposure, 652.4 (454.8) days; median, 588.0 days
- The 4 most common reasons for discontinuation were withdrawal by patient (25.4%), other (17.6%; including discontinuation due to the Ukraine-Russia conflict), AEs (8.4%), and lost to follow-up (7.1%)

Table 1. Demographics and Baseline Clinical Characteristics[a]

Characteristics	All Patients (N=523)
Age,[b] mean (SD), years	35.1 (12.2)
Male, n (%)	322 (61.6)
Race, n (%)	
White	380 (72.7)
Black or African American	126 (24.1)
Asian/other[c]	17 (3.3)
Diagnosis	
Schizophrenia/schizophreniform disorder[d]	475 (90.8)
Bipolar I disorder	48 (9.2)
Weight, mean (SD), kg	77.4 (15.5)
BMI, mean (SD), kg/m²	26.0 (4.3)
CGI-S score, mean (SD)	3.1 (0.9)

[a]Based on all patients who received ≥1 dose of OLZ/SAM.
[b]Age is based on data collected at time of screening in the patient's initial randomized controlled trial.
[c]"Other" includes patients who were American Indian or Alaska Native individuals, those reporting multiple races, and those responding "other."
[d]15 patients with a diagnosis of schizophreniform disorder were enrolled.
BMI, body mass index; CGI-S, Clinical Global Impression–Severity; OLZ/SAM, combination olanzapine and samidorphan.

Safety

Table 2. Summary of Adverse Events[a]

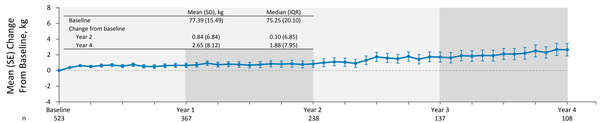
Category[b]	All Patients (N=523)
Any AE, n (%)	314 (60.0)
AEs by highest severity, n (%)	
Mild	143 (27.3)
Moderate	148 (28.3)
Severe	23 (4.4)
AEs leading to discontinuation, n (%)	44 (8.4)
Any SAE, n (%)	35 (6.7)
SAE leading to death,[c] n (%)	1 (0.2)
Most common AEs (≥5% of patients)	
Weight increased	51 (9.8)
Headache	37 (7.1)
Anxiety	32 (6.1)
Insomnia	31 (5.9)
Somnolence	31 (5.9)
Nausea	30 (5.7)
Weight decreased	30 (5.7)

[a]All patients who received ≥1 dose of OLZ/SAM.
[b]Any patient who experienced >1 AE in a category was counted only once in that category.
[c]One SAE resulted in death during the study (completed suicide). The suicide was ruled "definitely not related" to treatment with OLZ/SAM by the study investigator.
AE, adverse event; OLZ/SAM, combination olanzapine and samidorphan; SAE, serious adverse event.

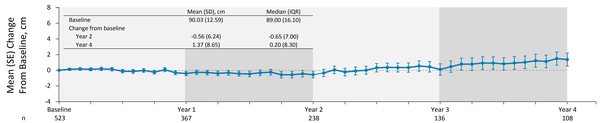
Weight and Waist Circumference

Figure 2. Change From Baseline in Body Weight and Waist Circumference

A. Body Weight



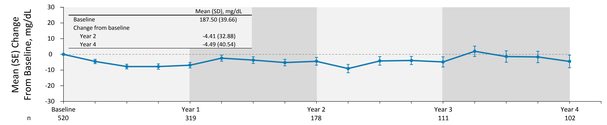
B. Waist Circumference



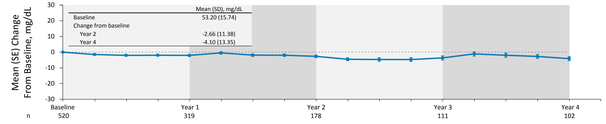
Metabolic Effects

Figure 3. Change From Baseline in Metabolic Parameters

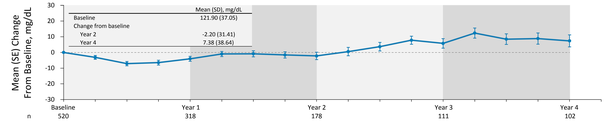
A. Total Cholesterol



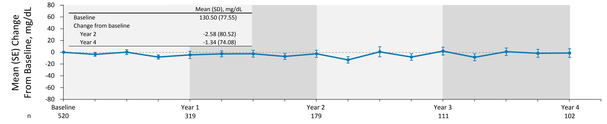
B. HDL Cholesterol



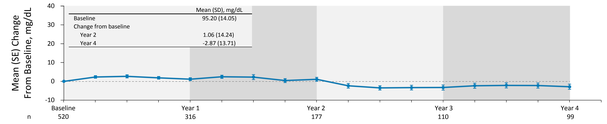
C. LDL Cholesterol



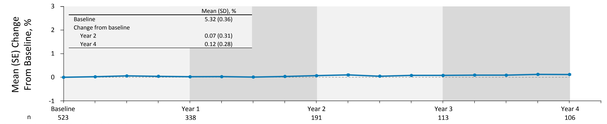
D. Triglycerides



E. Glucose



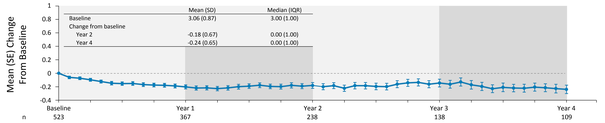
F. HbA_{1c}



HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Durability of OLZ/SAM Treatment Effect

Figure 4. Change From Baseline in CGI-S Score



CGI-S, Clinical Global Impression–Severity.

LIMITATIONS

- Lack of a comparator arm limits interpretation of efficacy and safety
- Missing data due to patients who discontinued may have affected the findings
- In addition, patients with a less favorable outcome may have dropped out of the antecedent trial, creating potential selection bias
- Patient baseline characteristics in this study may have varied because of differences in inclusion and exclusion criteria of the 3 antecedent studies
- Fasting status at the time of collection for metabolic laboratory parameters was based solely on self-report

CONCLUSIONS

- In this open-label extension study, 53.7% (242/451) of eligible patients received ≥2 years of treatment, and 32.5% (109/335) received 4 years of treatment
- OLZ/SAM maintained symptom control and had a long-term safety profile over 4 years that was consistent with past observations of OLZ/SAM use[6-10] in patients with schizophrenia or BD-I
  - Small changes in body weight
  - Minimal changes in waist circumference
  - Minimal changes in metabolic parameters
- These results highlight the long-term safety and clinical benefits of OLZ/SAM for the maintenance treatment of schizophrenia and BD-I

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AUTHOR DISCLOSURES

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