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# Long-Term Safety, Tolerability, and Durability of Treatment Effect of Olanzapine and Samidorphan:

## Results of a 4-Year Open-Label Study

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## Abstract

**Objective:** Evaluate long-term safety, tolerability, and durability of the effect of olanzapine/samidorphan (OLZ/SAM) for up to 4 years in patients with schizophrenia, schizophreniform disorder, or bipolar I disorder (BD-I).

**Methods:** This phase 3, multicenter, open-label, long-term extension (conducted June 2017–September 2023) assessed OLZ/SAM in patients completing the ENLIGHTEN clinical program. Patients received ≥2–4 years of additional treatment. Safety assessments included adverse event (AE) incidences and changes from baseline in body weight, waist circumference, and lipid/glycemic parameters. The durability of the effect was assessed using the Clinical Global Impressions–Severity (CGI-S) scale.

**Results:** Of 524 patients enrolled, 523 received ≥1 dose of OLZ/SAM. Of these, 460 (88%) patients had schizophrenia, 15 (3%) had schizophreniform disorder, and 48 (9%) had BD-I. Mean (SD) age was 35.1 (12.2) years. Mean (SD) OLZ/SAM exposure was 652.4 (454.8) days. Of 451 patients eligible for 2 years of treatment, 242 (53.7%) received it; of 335 patients eligible for 4 years, 109 (32.5%) received it. The most common AEs were weight increased (9.8%), headache (7.1%), anxiety (6.1%), insomnia (5.9%), somnolence (5.9%), nausea (5.7%), and weight decreased (5.7%). At 2 years, mean (SD) body weight change was 0.84 (6.84) kg; waist circumference change was −0.56 (6.24) cm. At 4 years, mean (SD) body weight change was 2.65 (8.12) kg; waist circumference change was 1.37 (8.65) cm. Changes in lipid/glycemic parameters were minimal. CGI-S scores remained stable.

**Conclusion:** OLZ/SAM maintained symptom control with a long-term safety profile over 4 years consistent with that of prior studies.

**Trials Registration:** ClinicalTrials.gov identifier: NCT03201757.


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Antipsychotic medications are recommended treatments for the management of schizophrenia and bipolar I disorder (BD-I)[1–4] because they confer several noted benefits, including reducing acute symptoms and lowering the risk of relapse and hospitalization.[5–8] Many of these medications, however, are associated with weight gain and metabolic changes that raise safety and tolerability concerns,[9–13] especially given that long-term treatment for these conditions is generally required. Olanzapine is among the most efficacious of the atypical antipsychotics used for the treatment of schizophrenia and BD-I, and its use is associated with reductions in relapse rates and hospitalizations.[14–17] However, despite olanzapine's well-known benefits, the clinical utility of olanzapine has been limited by its propensity to cause weight gain and adverse cardiometabolic effects such as type 2 diabetes, dyslipidemia, and metabolic syndrome.[9,12,18–23]

A combination of olanzapine and samidorphan (OLZ/SAM) provides the established antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain.[24,25] Based on results from the ENLIGHTEN clinical trial program and related open-label studies (see Supplementary Materials), OLZ/SAM treatment is associated with clinical symptom stability and with significantly less weight gain than with olanzapine monotherapy.[24–27] A remaining question, however, was how well OLZ/SAM could provide symptom control and weight gain mitigation over an extended time, consistent with the long-term treatment needs of patients with schizophrenia or BD-I.

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## Clinical Points

- In this open-label extension of 523 patients with schizophrenia (n = 460, 88%), schizophreniform disorder (n = 15, 3%), or bipolar I disorder (n = 48, 9%), clinical symptoms remained stable for up to 4 years of olanzapine/samidorphan (OLZ/SAM) treatment.
- Treatment with OLZ/SAM was associated with small changes in body weight at 2 years (0.84 kg) and 4 years (2.65 kg).
- Changes in lipid/glycemic parameters were minimal.

The current study represents the culmination of the ENLIGHTEN clinical trial program and builds on those earlier observations. The objective of this study was to evaluate the long-term safety, tolerability, and durability of treatment effect of OLZ/SAM, including characterization of its weight and metabolic profiles in patients with up to 4 years of open-label treatment.

## METHODS

This study (ClinicalTrials.gov identifier: NCT03201757) was conducted from June 15, 2017, to September 6, 2023, in accordance with Good Clinical Practice principles (International Conference on Harmonisation, 1997) and ethical principles derived from the Declaration of Helsinki and in accordance with local regulations. The protocol and all amendments were approved by an institutional review board or ethics committee at each study site. All patients provided written informed consent before study entry.

### Study Design and Treatments

This phase 3, 2- to 4-year (48-month), multicenter, open-label study was conducted at a total of 90 sites: 45 sites within the United States and 45 sites in countries including Austria, Bulgaria, Ireland, Israel, Italy, Poland, Russia, Serbia, South Korea, Ukraine, and the United Kingdom. Eligible patients were enrolled within 7 days of completing 1 of 3 antecedent phase 3 clinical trials investigating OLZ/SAM (Figure 1). Two of the preceding studies[26,27] (NCT02669758 and NCT02873208) were 52-week, open-label, rollover extensions of phase 3 pivotal randomized controlled trials in adults with schizophrenia (NCT02634346 and NCT02694328). The third study[25] (NCT03187769) was a 12-week randomized controlled trial comparing OLZ/SAM with olanzapine in young adults with recent-onset schizophrenia, schizophreniform disorder, or BD-I.

This study was designed initially with a treatment period of 2 years; however, the protocol was subsequently amended to extend the potential OLZ/SAM treatment duration to 4 years. Maximum treatment duration also varied by patient, as the study end date was scheduled to occur 24 months after the date that the last patient was enrolled. Therefore, the treatment duration for which each patient was eligible depended on their enrollment date relative to that time point. Study visits were scheduled monthly. In some cases, visits were conducted remotely because of the COVID-19 pandemic or the Ukraine-Russia conflict, which disrupted patients' ability to travel to certain study sites. However, the final visit was required to be in person. The 2- to 4-year treatment period was followed by a 4-week safety follow-up period.

Patients received daily oral OLZ/SAM for up to 4 years. The olanzapine dosage in OLZ/SAM was 5, 10, 15, or 20 mg; the dosage of samidorphan was fixed at 10 mg. Patients started the study taking the same daily oral dose of OLZ/SAM taken in their antecedent study or an OLZ/SAM dose that matched the olanzapine equivalent taken in the antecedent study. Dose adjustments were allowed after the start of the study at the investigator's discretion.

### Patients

All enrolled patients met the eligibility criteria of the OLZ/SAM randomized controlled trial that they had originally entered. The entry criteria for each are reported in detail in the primary publications for those respective trials (ENLIGHTEN-1[28]; ENLIGHTEN-1 extension[27]; ENLIGHTEN-2[24]; ENLIGHTEN-2 extension[26]; ENLIGHTEN-Early[25]) and in Supplementary Materials.

### Assessments

The durability of the OLZ/SAM treatment effect was assessed using the change from baseline in the Clinical Global Impression–Severity (CGI-S) scale[29] and the time to study discontinuation. Negative scores on the CGI-S indicate clinical symptom improvement.

Safety end points included the incidence and severity of adverse events (AEs) and changes from baseline in body weight and waist circumference, each assessed at monthly visits. Weight and waist circumference were measured at each in-person assessment. Quarterly laboratory evaluations included fasting lipid (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol, and triglycerides) and glycemic (glucose and glycosylated hemoglobin [$HbA_{1c}$]) parameters. Fasting status (≥8 hours before blood draw) was based on patient self-report. Additionally, vital signs and electrocardiograms (ECGs) were assessed quarterly. When visits were conducted remotely, data for in-person measures, including weight, waist circumference, and clinical laboratory parameters, were not available.

### Statistical Analysis

All analyses were conducted on data from all enrolled patients who received ≥1 dose of OLZ/SAM. For each


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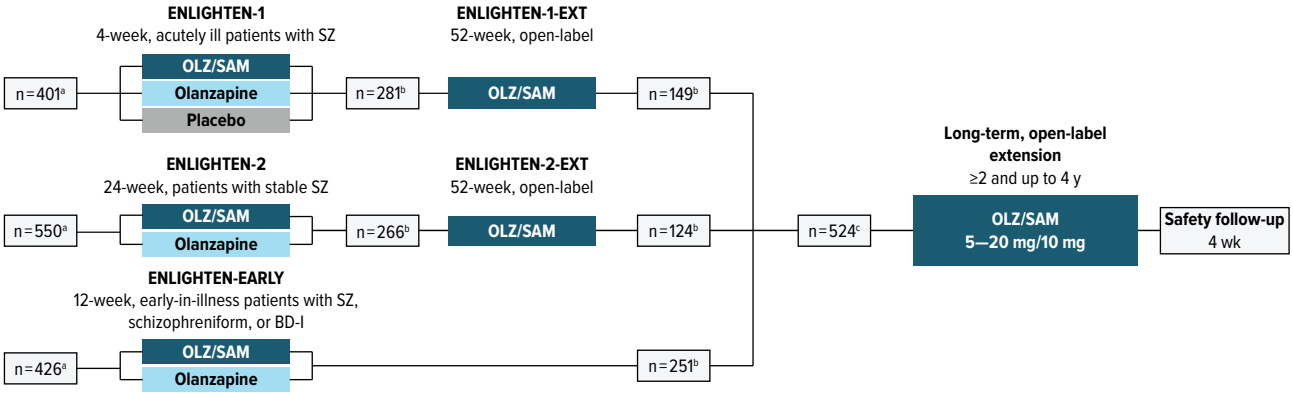
Figure 1.
## Study Design




[a]Number of patients who entered antecedent studies. [b]Number of patients who continued from antecedent study into extension. [c]Number of patients who entered the current long-term, open-label extension.
Abbreviations: BD-I = bipolar I disorder, EXT = extension, OLZ/SAM = combination of olanzapine and samidorphan, SZ = schizophrenia.

end point, baseline was defined as the last nonmissing assessment before the first dose of OLZ/SAM in the current study.

All results, including demographics and baseline clinical characteristics, were summarized using descriptive statistics on observed data with no imputation of missing values. Adverse events were coded using Medical Dictionary for Regulatory Activities (Version 26.0) preferred terms; incidence and severity of AEs, serious AEs (SAEs), and AEs leading to study discontinuation were summarized. Changes from baseline in metabolic parameters were summarized by quarterly visit. Changes from baseline in CGI-S scores, body weight, and waist circumference were summarized by monthly visit. Time to discontinuation was estimated using the Kaplan-Meier method.

# RESULTS

## Patients and Disposition

Of the 524 patients enrolled in the study, 523 received ≥1 dose of OLZ/SAM and were included in the analysis. Overall, 72 patients discontinued the study due to the Ukraine-Russia conflict, leaving a total of 451 patients who were eligible to receive at least 2 years of OLZ/SAM treatment, with 242 (53.7%) reaching that time point. A total of 335 patients were eligible to receive 4 years of treatment, and 109 (32.5%) reached that time point. The 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%). The mean (SD) duration of exposure to OLZ/SAM for all patients enrolled in the study was 652.4 (454.8) days (median, 588.0 days).

Table 1.
## Demographics and Baseline Clinical Characteristics[a]

| Characteristics | All patients (N = 523) |
|---|---|
| **Age,[b] mean (SD), y** | 35.1 (12.2) |
| **Sex, n (%)** | |
| Male | 322 (61.6) |
| Female | 201 (38.4) |
| **Race, n (%)** | |
| White | 380 (72.7) |
| Black or African American | 126 (24.1) |
| Asian | 8 (1.5) |
| Other or multiple races[c] | 9 (1.7) |
| **Region, n (%)** | |
| US | 206 (39.4) |
| Non-US | 317 (60.6) |
| **Weight, mean (SD), kg** | 77.4 (15.5) |
| **Waist circumference, mean (SD), cm** | 90.0 (12.6) |
| **BMI, mean (SD), kg/m²** | 26.0 (4.3) |
| **Diagnosis, n (%)** | |
| Schizophrenia | 460 (88) |
| Bipolar I disorder | 48 (9) |
| Schizophreniform disorder | 15 (3) |
| **CGI-S score, mean (SD)** | 3.06 (0.87) |

[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]A patient who reported >1 race is counted once under this category.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impression–Severity, OLZ/SAM = combination of olanzapine and samidorphan.

Demographic and baseline characteristics are presented in Table 1. Most patients were male (61.6%) and White (72.7%) and were enrolled predominantly from non-US sites (60.6%). Most patients who were enrolled were diagnosed with schizophrenia (88%) or BD-I (9%). The mean (SD) age at baseline was 35.1 (12.2) years. The mean (SD) baseline weight was

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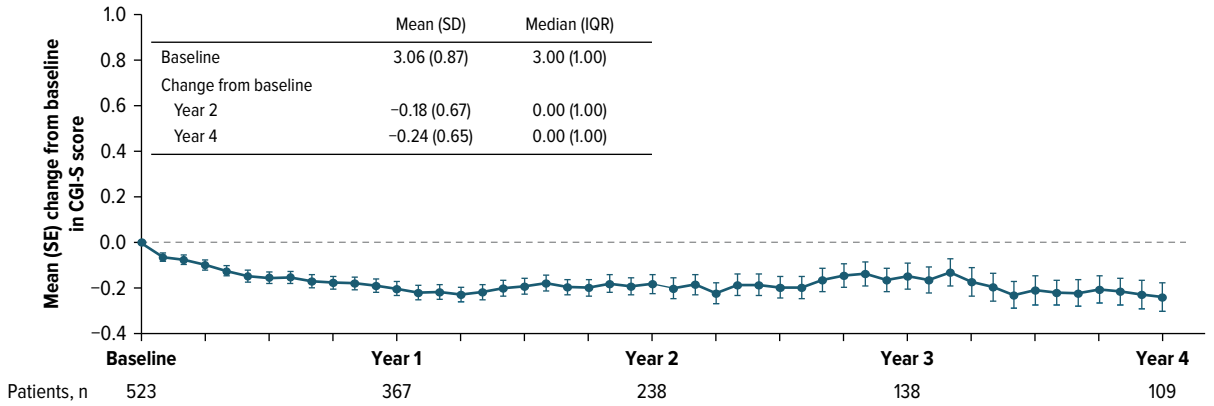
Figure 2.
**Change From Baseline[a] in CGI-S Score (Observed Cases)**




[a]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.
Abbreviation: CGI-S = Clinical Global Impression–Severity.

77.4 (15.5) kg (median [interquartile range (IQR)], 75.3 [20.1]), while that of waist circumference was 90.0 (12.6) cm (median [IQR], 89.0 [16.1]). Patients had a mean (SD) body mass index (BMI) of 26.0 (4.3) kg/m$^2$ at study entry, with 1.9% being underweight (BMI <18.5 kg/m$^2$), 44.2% of normal weight (BMI 18.5 to <25 kg/m$^2$), 35.9% overweight (BMI ≥25 to <30 kg/m$^2$), and 18.0% obese (BMI ≥30 kg/m$^2$). Illness severity was mild at baseline, with a mean (SD) CGI-S score of 3.1 (0.9) (median [IQR], 3.0 [1.0]). The mean dose of OLZ/SAM was 14.1/10 mg/d. Overall, 45.3% of patients received a modal OLZ/SAM dose of 20/10 mg, and 29.2% received a modal dose of 10/10 mg.

## Durability of Treatment Effect

At 2 years, the mean (SD) change from baseline CGI-S score was −0.18 (0.7) (median [IQR], 0.0 [1.0]) and at 4 years was −0.24 (0.7) (median [IQR], 0.0 [1.0]) (Figure 2). The median (95% CI) time to study discontinuation was 588.0 (504.0, 672.0) days.

## Safety

**Adverse events.** A summary of AEs that occurred in ≥5% of patients is presented in Table 2. Overall, 314/523 (60.0%) patients reported an AE during the treatment period. Most AEs were mild or moderate in severity. The most common AEs were weight increased (9.8%), headache (7.1%), anxiety (6.1%), insomnia (5.9%), somnolence (5.9%), nausea (5.7%), and weight decreased (5.7%). In total, 44 (8.4%) patients discontinued due to an AE. The most common AE leading to discontinuation was increased weight (8 [1.5%]), followed by $HbA_{1c}$ increased (6 [1.1%]) and exacerbation of schizophrenia (6 [1.1%]). Severe AEs were experienced by 23 (4.4%) patients. Except for exacerbation of schizophrenia, which occurred in 2 (0.4%) patients, no other severe AE was reported in >1 (0.2%) patient each.

Table 2.
**Summary of Adverse Events[a]**

| Category[b] | All patients (N = 523) |
|---|---|
| **Any AE, n (%)** | 314 (60.0) |
| **AE by highest severity, n (%)** | |
| Mild | 143 (27.3) |
| Moderate | 148 (28.3) |
| Severe | 23 (4.4) |
| **AEs leading to discontinuation** | 44 (8.4) |
| **Any SAE** | 35 (6.7) |
| **SAE leading to death[c]** | 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]Patients who experienced >1 AE in a category were counted only once in that category.
[c]One SAE resulted in death during the study (completed suicide); see "Safety" for details.
Abbreviations: AE = adverse event, OLZ/SAM = combination of olanzapine and samidorphan, SAE = serious adverse event.

In total, 35 (6.7%) patients experienced an SAE during the treatment period. The SAEs reported in >1 patient were exacerbation of schizophrenia (11 [2.1%]) and anxiety (2 [0.4%]).

Five (1.0%) patients experienced ≥1 AE involving the potential for suicidal ideation or behavior, including 2 (0.4%) with an AE of suicidal ideation and 1 (0.2%) each


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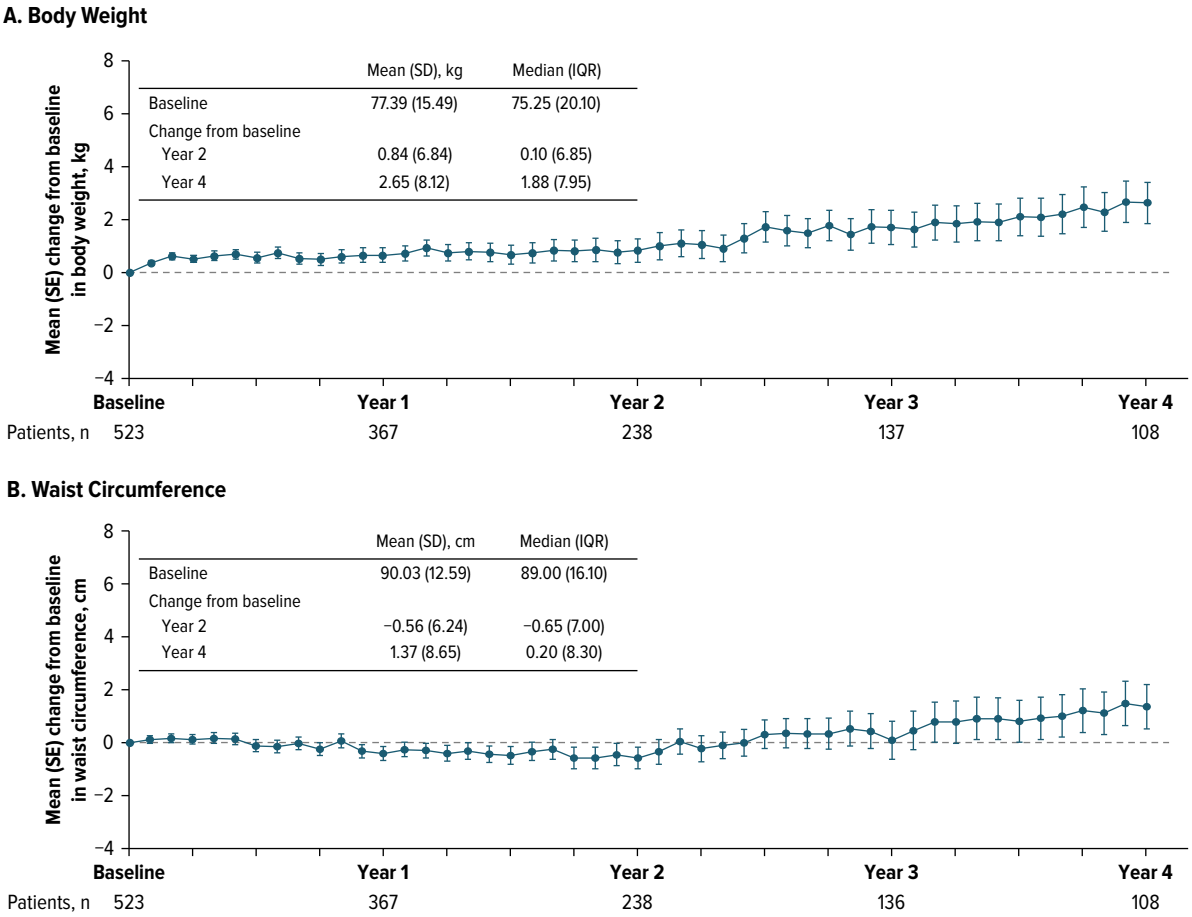
Figure 3.

## Change From Baseline[a] in Body Weight and Waist Circumference (Observed Cases)




[a]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.

with an AE of suicidal depression, suicide attempt, or completed suicide. One patient, a 20-year-old white female with a diagnosis of schizophrenia, died by suicide. The patient missed OLZ/SAM doses for 3 consecutive days before the suicide occurred. The investigator assessed the completed suicide as not related to OLZ/SAM.

**Weight change.** For patients who contributed data to the 2-year assessment, the observed mean (SD) change in absolute body weight from baseline was 0.84 (6.8) kg (median [IQR], 0.10 [6.9]) kg (Figure 3A); the mean (SD) percent change in body weight was 1.12% (8.6%). The mean (SD) change in waist circumference was −0.56 (6.2) cm (median [IQR], −0.65 [7.0]) cm (Figure 3B). For patients who received 4 years of treatment, the observed mean (SD) change from baseline in body weight was 2.65 (8.1) kg (median [IQR], 1.88 [8.0]) kg (Figure 3A); the mean (SD) percent change in body weight was 3.54% (10.3%). The mean (SD) change in waist circumference was 1.37 (8.7) cm (median [IQR], 0.20 [8.3]) cm (Figure 3B).

Overall, the proportion of patients with a clinically significant weight gain of ≥7% at any time during the study was 32.7% (167/510), whereas the proportion of those with weight loss of ≥7% was 26.9% (137/510).

**Lipid and glycemic parameters.** Mean changes in lipid and glycemic parameters are shown in Figure 4. At 2 years, the mean (SD) change from baseline in total cholesterol was −4.41 (32.9) mg/dL, in HDL cholesterol was −2.66 (11.4) mg/dL, in LDL cholesterol was −2.20 (31.4) mg/dL, and in triglycerides was −2.58 (80.5) mg/dL. The mean (SD) change in $HbA_{1c}$ was 0.07% (0.3%) at 2 years, while that for fasting glucose concentration was 1.06 (14.2) mg/dL.

At 4 years, the mean (SD) change from baseline in total cholesterol was −4.49 (40.5) mg/dL, in HDL cholesterol was −4.10 (13.4) mg/dL, in LDL cholesterol was 7.38 (38.6) mg/dL, and in triglycerides was −1.34 (74.1) mg/dL. The mean (SD) change from baseline in $HbA_{1c}$ was 0.12% (0.3%) at 4 years, while that for fasting glucose concentration was 2.87 (13.7) mg/dL.

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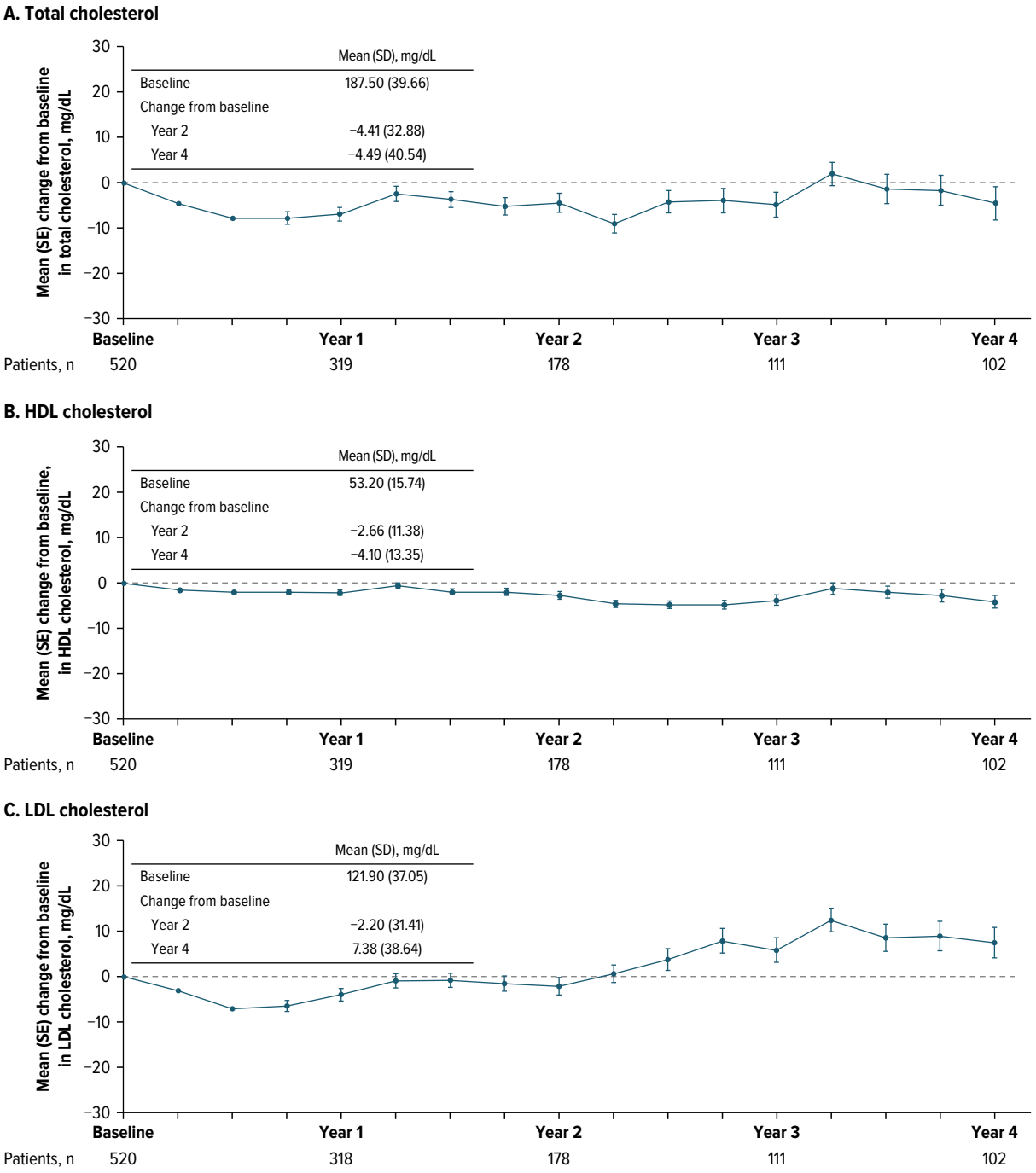
Figure 4.

## Change From Baseline[a] in Metabolic Parameters (Observed Cases)




[a]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.
Abbreviations: $HbA_{1c}$ = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

**Clinical laboratory parameters and other safety measures.** Mean changes in hematology parameters were small and not considered clinically meaningful. In assessments of liver function, no patients met Hy's Law criteria. No unexpected clinically meaningful changes in vital signs or ECG results were observed.

## DISCUSSION

In this open-label extension study, treatment with OLZ/SAM over a period of up to 4 years maintained symptom control in patients with schizophrenia, schizophreniform disorder, or BD-I, with a long-term



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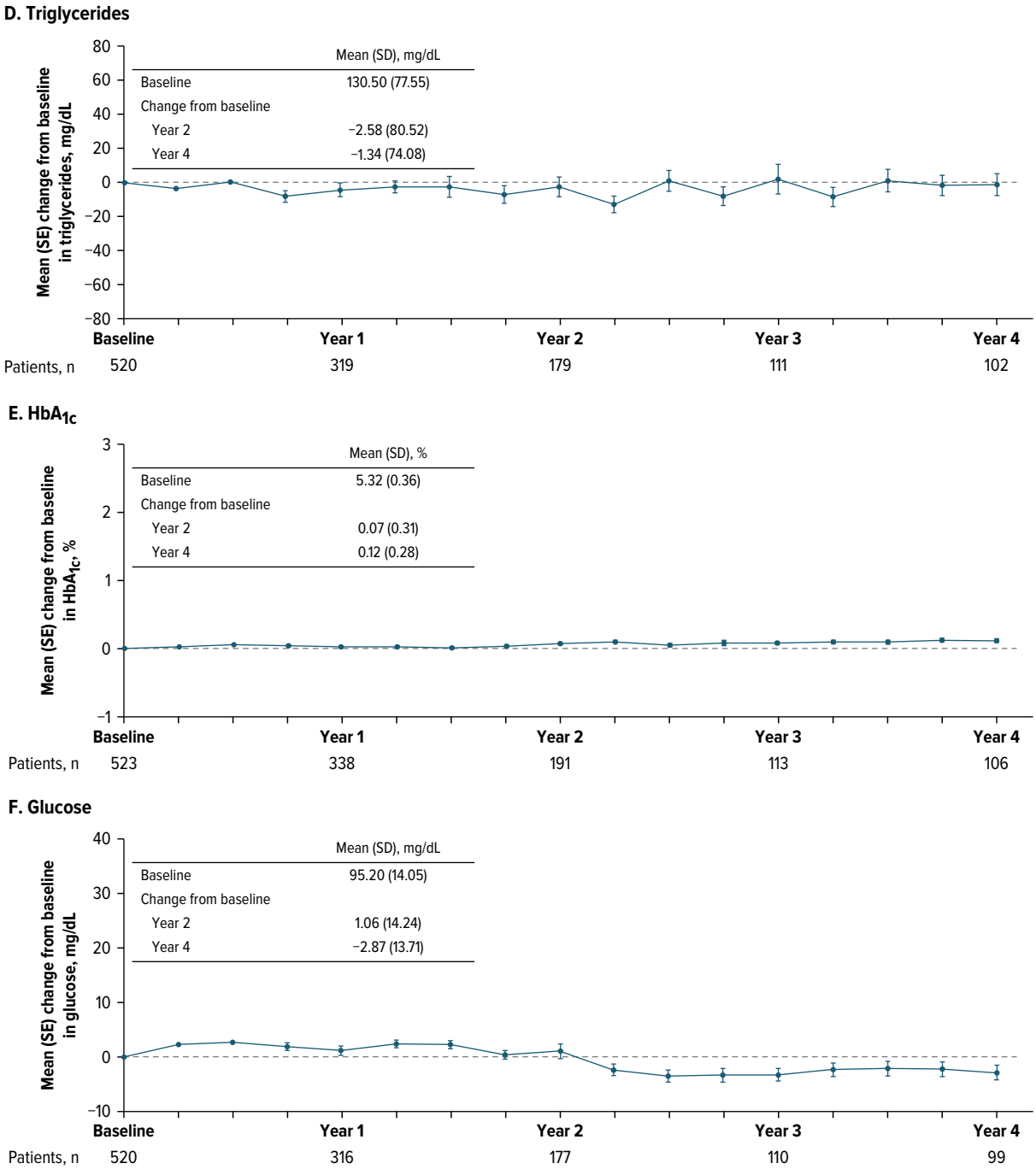
Figure 4.
**(Continued).**




safety profile that was consistent with that observed in previous studies in the ENLIGHTEN program.[24–28] Overall, the majority of AEs were mild or moderate in severity, and SAEs were infrequent. OLZ/SAM was associated with small changes in body weight, minimal changes in waist circumference, and minimal changes in lipid and glycemic parameters. No unexpected clinically meaningful changes in laboratory parameters, vital signs, or ECG results were observed.

Treatment with OLZ/SAM was associated with a durable antipsychotic treatment effect. Approximately half of the patients in the current study enrolled after completing 52 weeks of open-label OLZ/SAM treatment, whereas the other half enrolled after completing 12 weeks

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of active treatment with either olanzapine or OLZ/SAM. Thus, patients' clinical symptoms were generally well controlled at entry into the current study and remained so with continued OLZ/SAM treatment.

Importantly, patients stayed on OLZ/SAM for an extended period of time, with a median duration of exposure of 1.6 years. Previous studies have demonstrated longer patient retention on olanzapine compared with other antipsychotics, suggestive of its antipsychotic efficacy.[14,30] In Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the rate of all-cause discontinuation with olanzapine was 64% over 1.5 years.[14] Similarly, in a study of patients with first-episode psychosis, the discontinuation rate with olanzapine was 69% over 3 years.[30] The rate of all-cause discontinuation with OLZ/SAM over 4 years in this study was 64%, although the observational period was longer than that of previous studies, thus providing a unique opportunity to assess the clinical benefits of OLZ/SAM treatment as maintenance therapy. Over half of the patients who were eligible for 2 years of treatment reached that time point, and nearly one-third of the patients eligible for 4 years of treatment reached that time point, for a total OLZ/SAM exposure (current plus antecedent study) of 5 years or more for some patients. These retention rates are notable given the dual challenges of the COVID-19 pandemic and the Ukraine-Russia conflict that occurred during the study.

The small amount of weight gained and minimal waist circumference changes observed during treatment with OLZ/SAM, at both the 2- and 4-year exposure time points, are important results for both clinicians and patients, given the propensity of olanzapine monotherapy to cause weight gain.[14,31,32] Most of the weight gain associated with OLZ/SAM exposure occurred in the antecedent studies (4-week pivotal study, mean +3.02 kg[28]; 24-week pivotal study, mean +3.18 kg[24]), with smaller changes at the 2- and 4-year exposure time points in the current study. In an analysis of studies ≥48 weeks long, the mean weight gained on olanzapine was 5.6 kg,[33] more than double the amount observed with OLZ/SAM after 4 years in this study. Although there are no available studies in a similar population against which weight gain can be compared, a prospective study was identified that included over 120,000 US adults free of chronic diseases and not obese at baseline.[34] In that study, where weight was assessed in 4-year increments between 1986 and 2006, participants gained an average of 1.52 kg (5th–95th percentiles, −1.9 to 5.6 kg) within each 4-year period.[34]

The minimal changes observed in metabolic parameters were generally consistent with those found in previous studies of OLZ/SAM.[24–28] In a post hoc analysis of the 24-week ENLIGHTEN-2 study comparing OLZ/SAM with olanzapine, OLZ/SAM significantly reduced the risk of developing stage 1/2 hypertension by 52%, obesity by 48%, and metabolic syndrome by 45% compared with olanzapine.[35] The small changes in lipid and glycemic parameters observed in the current study with OLZ/SAM treatment are encouraging because patients with serious mental illness are already at an increased risk of cardiovascular disease and metabolic abnormalities compared with the general population,[3,36,37] and efforts to reduce this risk while still providing effective treatment are central to good clinical management of these serious conditions. These results indicate that OLZ/SAM maintained symptom control while mitigating weight gain and metabolic abnormalities, making OLZ/SAM a suitable long-term treatment option for people living with schizophrenia or BD-I.

### Limitations

These results should be interpreted within the context of the study's limitations. Because the study had an open-label design, it did not include a comparator arm, which may limit interpretations of safety and efficacy data. Approximately half of patients discontinued before 2 years and about two-thirds before 4 years; thus, missing data may have affected the results reported here. In addition, patients with a less favorable outcome may have dropped out of their antecedent study, creating the potential for selection bias. Also, patient baseline characteristics in this study may be variable because of differences in the inclusion and exclusion criteria of the 3 antecedent studies. Lastly, fasting status was based solely on self-report and not confirmed.

## CONCLUSION

In this open-label extension study lasting up to 4 years, OLZ/SAM treatment was well tolerated with a safety profile consistent with that of previous studies in the ENLIGHTEN clinical program. Despite the disruptions related to the global COVID-19 pandemic and the Ukraine-Russia conflict, a significant number of patients remained on long-term treatment with OLZ/SAM. Treatment with OLZ/SAM resulted in small changes in body weight, minimal changes in metabolic parameters, and stability in clinical symptoms over the course of therapy. Overall, these results highlight the long-term safety and clinical benefits of OLZ/SAM for the maintenance treatment of schizophrenia and BD-I.

## Article Information

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# Supplementary Material

**Article Title:** Long-Term Safety, Tolerability, and Durability of Treatment Effect of Olanzapine and Samidorphan: Results of a 4-Year Open-Label Study

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## LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. Supplementary Text: The Enlighten Program

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# SUPPLEMENTARY MATERIAL

## Supplementary Text: The ENLIGHTEN Program

### Results of the ENLIGHTEN Clinical Trials Program

The ENLIGHTEN clinical trial program was a series of phase 3, randomized, double-blind studies that tested antipsychotic efficacy and safety outcomes in patients treated with combined olanzapine and samidorphan (OLZ/SAM) versus olanzapine.[1-3] Overall, OLZ/SAM treatment was associated with disease improvement similar to that of olanzapine across studies.[1-3] In studies of ≥12 weeks' duration, treatment with OLZ/SAM was associated with significantly less weight gain than was olanzapine.[2,3] Although OLZ/SAM was associated with some degree of weight gain initially, weight stabilized after 4 to 6 weeks of OLZ/SAM treatment, while patients taking olanzapine monotherapy continued to gain weight.[2-4] Furthermore, in the ENLIGHTEN program's open-label extension studies, OLZ/SAM was associated with long-term stability of clinical symptoms and weight for up to 1 year of treatment.[5,6]

### Summary of ENLIGHTEN Clinical Trial Criteria

ENLIGHTEN-1 and ENLIGHTEN-2 enrolled adult patients (aged 18–70 or 18–55 years, respectively) who met criteria for a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[7] (DSM-5) diagnosis of schizophrenia and had a baseline body mass index (BMI) between 18 and 40 kg/m$^2$ or 18 and 30 kg/m$^2$, respectively.[1,2] Enrollment criteria for ENLIGHTEN-Early were selected to capture patients who were early in the course of illness; eligible patients were between 16 and 40 years, had a primary DSM-5 diagnosis of schizophrenia, schizophreniform disorder, or bipolar I disorder and had a baseline BMI of <30 kg/m$^2$.[3] Patients who tested positive for any drug of abuse at study entry were excluded.

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