# Olanzapine and Samidorphan in Adults With Schizophrenia or Bipolar I Disorder: Updated Review of Clinical Data

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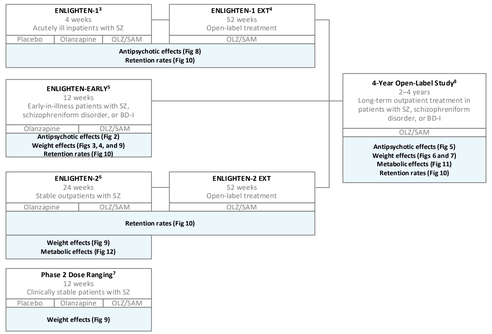
## BACKGROUND

- The combination of olanzapine and samidorphan (OLZ/SAM) received US Food and Drug Administration approval in 2021 for the treatment of schizophrenia and bipolar I disorder (BD-I) and was accompanied by a clinical data review summarizing OLZ/SAM research to date[1,2]
- In that review, data from 18 OLZ/SAM studies in >1600 patients characterized the pharmacokinetic, efficacy, and safety profile of OLZ/SAM
  - Clinical pharmacokinetic data supported the use of OLZ/SAM in patients with BD-I based on bioequivalence with olanzapine[2]
  - Antipsychotic efficacy and weight gain mitigation of OLZ/SAM were observed in multiple studies; effects were durable and maintained during open-label treatment[2]
- This review summarizes clinical studies and analyses of OLZ/SAM from the past 5 years, providing a comprehensive overview of the OLZ/SAM clinical program

**Figure 1.** Summary of Studies




**Analyses summarized in this poster[a]**

| | |
|---|---|
| ENLIGHTEN-EARLY[5] | • 12-week double-blind randomized study<br>• Effectiveness and safety of OLZ/SAM in early-in-illness patients with SZ, schizophreniform disorder, or BD-I |
| 4-Year Open-Label Study[8] | • Long-term safety and durability of treatment effect study with up to 4 years of additional OLZ/SAM treatment in patients with SZ, schizophreniform disorder, or BD-I |
| Individual patient data meta-analysis[5-7,9] | • Estimate of OLZ/SAM weight mitigation vs olanzapine at 12 weeks<br>• Includes 3 phase 2/3 clinical trials with weight as primary/secondary outcome:<br>– Phase 2 dose-ranging study<br>– ENLIGHTEN-2<br>– ENLIGHTEN-EARLY |
| Negative symptoms of SZ[3,4] | • Post hoc, pooled analysis of ENLIGHTEN-1 and ENLIGHTEN-1 EXT<br>• PANSS Total score and Positive, Negative, and General Psychopathology Subscale scores |
| Cardiometabolic risk factors[6, 10] | • Post hoc analysis of ENLIGHTEN-2<br>• Comparing OLZ/SAM vs olanzapine across multiple cardiometabolic risk factors |
| Retention rates in the phase 3 clinical program[3-6,8,11] | • Summary of retention rates in 6 phase 3 studies of OLZ/SAM |

## Safety

**Table 1.** In a 4-year open-label study, the safety profile of OLZ/SAM was consistent with that observed in previous ENLIGHTEN program studies[3,5,6]; most AEs were mild to moderate in severity and serious AEs were rare

| Most common AEs (≥5% of patients)[b,c] | All patients (N = 523) |
|---|---|
| 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]Limitations of each analysis can be found in their respective publications/presentations. [b]All patients who received ≥1 dose of OLZ/SAM. [c]Patients who experienced >1 AE in a category were counted only once in that category.
AE, adverse event; BD-I, bipolar I disorder; EXT, extension; OLZ/SAM, combination olanzapine and samidorphan; SZ, schizophrenia; PANSS, Positive and Negative Syndrome Scale.

## RESULTS

### Antipsychotic Effects

**Figure 2.** In early-in-illness patients, OLZ/SAM treatment was associated with clinical symptom improvements similar to those associated with olanzapine at 12 weeks[a]

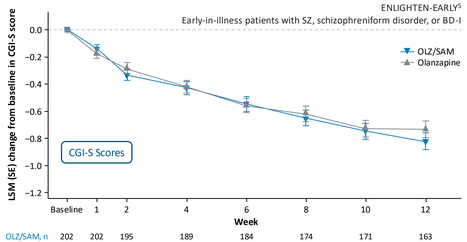



**Figure 5.** OLZ/SAM treatment was associated with durable antipsychotic effects over 4 years of OLZ/SAM open-label treatment[b]

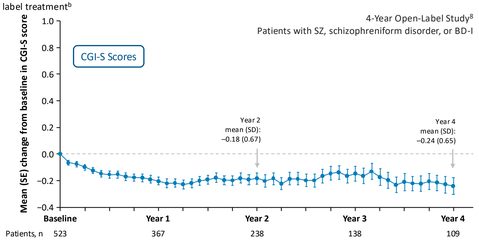
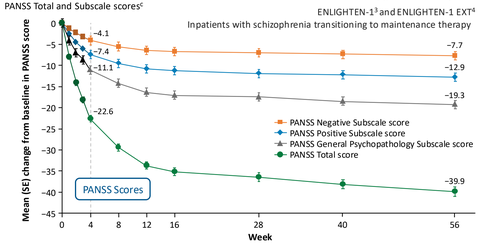



**Figure 8.** In a post hoc, pooled analysis, negative symptoms of schizophrenia decreased with OLZ/SAM treatment, and durable improvement was observed over 52 weeks of maintenance therapy, as assessed by PANSS Total and Subscale scores[c]




[a]Change from baseline to week 12 in CGI-S scores was a key secondary endpoint and was not formally tested due to early termination of the hierarchical testing procedure, which required statistical significance on the ≥10% weight gain endpoint before proceeding. [b]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study. [c]In the overall post hoc analysis population, defined as patients who had completed the 4-week ENLIGHTEN-1 lead-in study and had ≥1 postbaseline visit in the 52-week open-label ENLIGHTEN-1 Extension; the gray line represents end of the 4-week lead-in study and beginning of the extension study.
CGI-S, Clinical Global Impression–Severity; LSM, least squares mean; OLZ/SAM, combined olanzapine/samidorphan; PANSS, Positive and Negative Symptom Scale.

### Weight Effects

**Figure 3.** In early-in-illness patients, OLZ/SAM treatment was associated with significantly less weight gain vs olanzapine at 12 weeks[a]

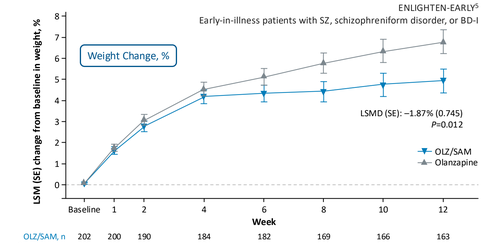



**Figure 6.** Small changes in body weight were observed for up to 4 years of OLZ/SAM open-label treatment[b]

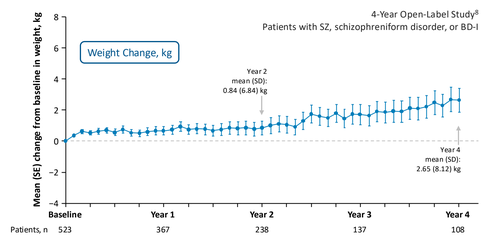
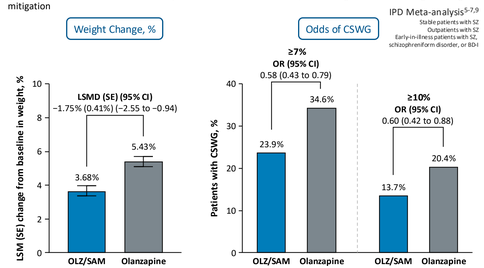



**Figure 9.** In an IPD meta-analysis across 3 clinical trials, OLZ/SAM was associated with significantly less weight gain and lower odds of CSWG vs olanzapine at 12 weeks of treatment, confirming consistent findings of weight mitigation




[a]Change from baseline to week 12 in body weight was the primary endpoint. [b]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.
CSWG, clinically significant weight gain; LSM, least squares mean; LSMD, LSM difference; OLZ/SAM, combined olanzapine/samidorphan; OR, odds ratio.

**Figure 4.** In early-in-illness patients, OLZ/SAM treatment was associated with a lower change from baseline in waist circumference vs olanzapine at 12 weeks[a]

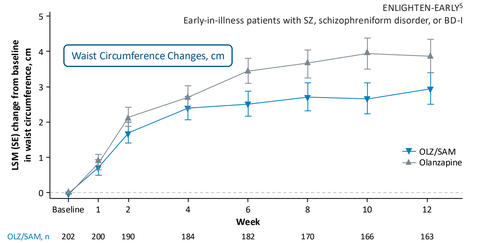
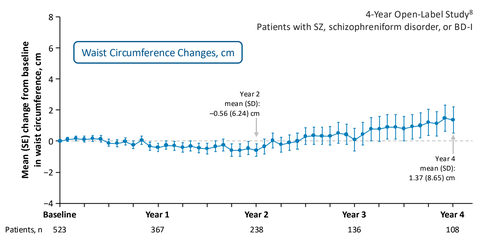
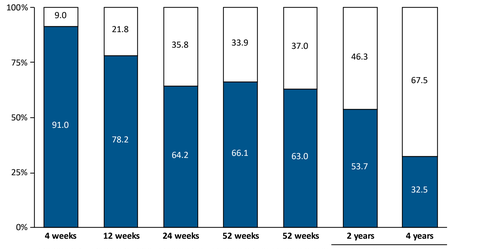



**Figure 7.** Minimal changes in waist circumference were observed for up to 4 years of OLZ/SAM treatment[b]




### Retention Rates in the Phase 3 Clinical Program[3-6,8,11]

**Figure 10.** Substantial retention rates were observed across the OLZ/SAM phase 3 clinical program




[a]Change from baseline to week 12 in waist circumference was a key secondary endpoint and was not formally tested due to early termination of the hierarchical testing procedure, which required statistical significance on the ≥10% weight gain endpoint before proceeding. [b]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.

## RESULTS (CON'T)

### Metabolic Effects

**Figure 11.** Changes in triglycerides and $HbA_{1c}$ were minimal following up to 4 years of OLZ/SAM open-label treatment

- Total, HDL, and LDL cholesterol and fasting glucose were stable over 4 years (not shown)

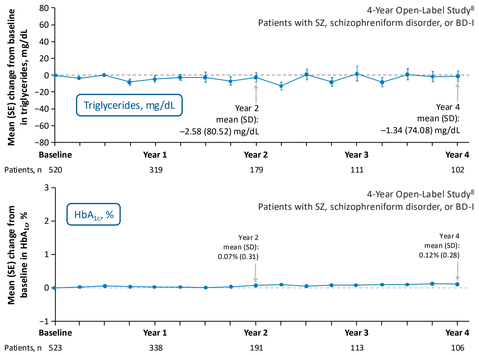
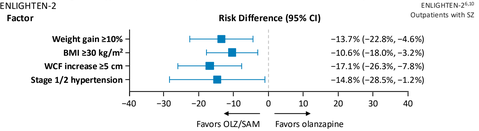



**Figure 12.** OLZ/SAM treatment reduced the risk of developing CSWG, obesity, ≥5 cm waist circumference increase, and stage 1/2 hypertension vs olanzapine over 24 weeks of treatment in this post hoc analysis of ENLIGHTEN-2




BMI, body mass index; CSWG, clinically significant weight gain; $HbA_{1c}$, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLZ/SAM, combined olanzapine/samidorphan; WCF, waist circumference.

## CONCLUSIONS

**Safety**
- The safety profile of OLZ/SAM was consistent with previous studies in the ENLIGHTEN program[3,5,6]

**Efficacy**
- The clinical symptom improvements observed in pivotal studies and associated open-label extensions remained stable in the 4-year open-label extension study[5]
  - Sustained symptom control was observed for up to 4 years of additional OLZ/SAM treatment, with some patients having up to 5 years of continuous OLZ/SAM exposure[8]
  - Negative symptoms of schizophrenia improved during short-term OLZ/SAM treatment, with continued improvement observed over 52 weeks of maintenance therapy[3,4]

**Weight and Metabolic Profile**
- OLZ/SAM treatment consistently resulted in significantly less weight gain vs olanzapine[5-7,9]; small changes in body weight and minimal changes in lipid/glycemic parameters were observed over long-term treatment[8]
  - OLZ/SAM treatment reduced the risk of developing clinically significant weight gain, obesity, waist circumference increase, and stage 1/2 hypertension vs olanzapine at 24 weeks[6,10]

**Patient Retention**
- Substantial retention rates were observed across the OLZ/SAM phase 3 clinical program[3-6,8]

**These results reinforce the clinical utility of OLZ/SAM as a long-term treatment option for patients with schizophrenia or BD-I**

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References, disclosure information, acknowledgments, and copies of this poster can be obtained through this QR (Quick Response) code.

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## DISCLOSURES

**LC** has served as consultant for AbbVie/Allergan, Acadia, Adamas, AdhereTech, Alkermes, Alumis, Angelini, Astellas, Autobahn, Avanir, Axsome, Biogen, BioXcel, Bristol-Myers Squibb, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Draig Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, MedAvante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, Wells Fargo, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; has served as a speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Bristol-Myers Squibb, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Neopharm, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, Vanda, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; owns stocks (small number of shares of common stock) in Bristol-Myers Squibb, Eli Lilly, J&J, Merck, and Pfizer (purchased >10 years ago) and stock options in Reviva; and receives royalties/publishing income from *Clinical Therapeutics* (through Spring 2025), Elsevier (Topic Editor, Psychiatry), Springer Healthcare (book), Taylor & Francis (Editor-in-Chief, *Current Medical Research and Opinion*, 2022-date), UpToDate (reviewer), and Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019).

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

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