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

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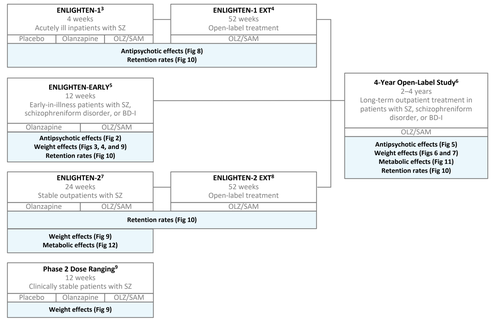
## BACKGROUND

- 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[6] | • 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[5,7,9,10] | • 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[4,9,11] | • 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[7,12] | • 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[3-8] | • Summary of retention rates in 6 phase 3 studies of OLZ/SAM |

[a]Limitations of each analysis can be found in their respective publications/presentations.
BD-I, bipolar I disorder; EXT, extension; OLZ/SAM, combined olanzapine/samidorphan; PANSS, Positive and Negative Syndrome Scale; SZ, schizophrenia.

## 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[3,5,7]; most AEs were mild to moderate in severity, and serious AEs were rare

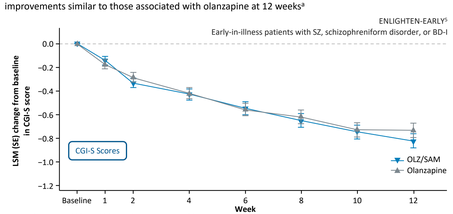
| Most common AEs (≥5% of patients)[a,b] | All patients (N = 523) |
|---|---|
| Weight increased | 51 (9.8) |
| Headache | 37 (7.1) |
| Anxiety | 32 (6.1) |
| Insomnia | 31 (5.9) |
| Somnolence | 31 (5.9) |
| Nausea | 30 (5.7) |
| Weight decreased | 30 (5.7) |

[a]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.
AE, adverse event; OLZ/SAM, combined olanzapine/samidorphan.

## RESULTS

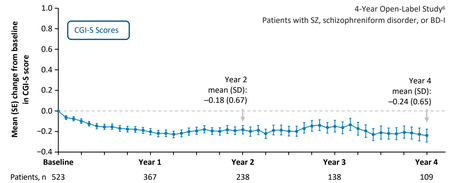
### Antipsychotic Effects

**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]



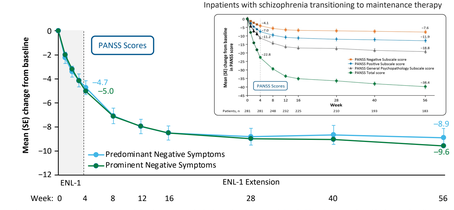

[a]Change from baseline to week 12 in CGI-S scores was a key secondary endpoint and was not formally tested due to early termination of the hierarchical testing procedure, which required statistical significance on the ≥10% weight gain endpoint before proceeding.
BD-I, bipolar I disorder; CGI-S, Clinical Global Impression–Severity; LSM, least squares mean; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

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




[a]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.
BD-I, bipolar I disorder; CGI-S, Clinical Global Impression–Severity; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

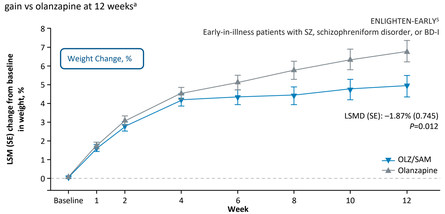
**Figure 8.** In a post hoc, pooled analysis, negative symptoms of schizophrenia decreased with OLZ/SAM treatment (inset)[11]; these effects were observed in subgroups of patients with predominant or prominent negative symptoms at baseline[a,b]




[a]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 dotted line represents end of the 4-week lead-in study and beginning of the extension study. [b]Prominent or high negative symptoms defined as a Marder Negative Factor score ≥24 at baseline. Predominant or high negative symptoms and low positive symptoms defined as a Marder Negative Factor score ≥24 at baseline; baseline score ≥4 on at least 2 of the following 3 PANSS items: blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6); and a PANSS *MoH* Positive Symptoms Factor score ≤19 at baseline (PANSS *MoH* Positive Factor: delusions [P1], hallucinatory behavior [P3], grandiosity [P5], suspiciousness/persecution [P6], and unusual thought content [G9]).
ENL-1, ENLIGHTEN-1; OLZ/SAM, combined olanzapine/samidorphan; PANSS, Positive and Negative Syndrome Scale.

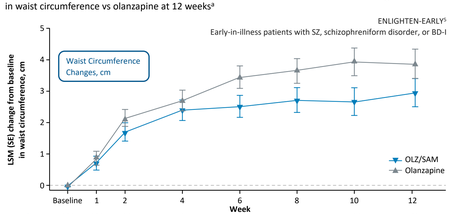
### Weight Effects

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



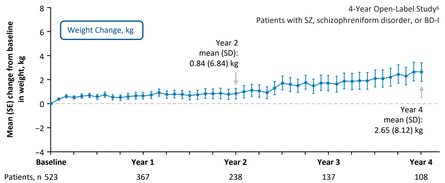

[a]Change from baseline to week 12 in body weight was the primary endpoint.
BD-I, bipolar I disorder; LSM, least squares mean; LSMD, LSM difference; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

**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]



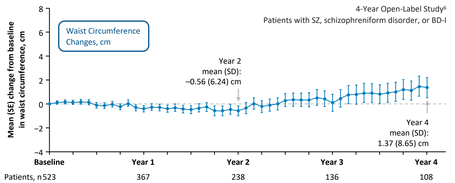

[a]Change from baseline to week 12 in waist circumference was a key secondary endpoint and was not formally tested due to early termination of the hierarchical testing procedure, which required statistical significance on the ≥10% weight gain endpoint before proceeding.
BD-I, bipolar I disorder; LSM, least squares mean; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

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



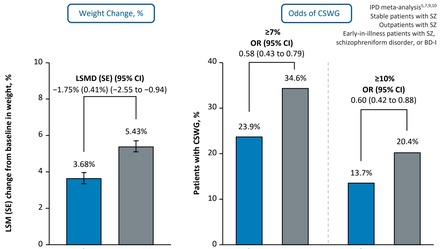

[a]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.
BD-I, bipolar I disorder; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

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




[a]Baseline was defined as the last nonmissing value before the first dose of study drug in the current study.
BD-I, bipolar I disorder; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

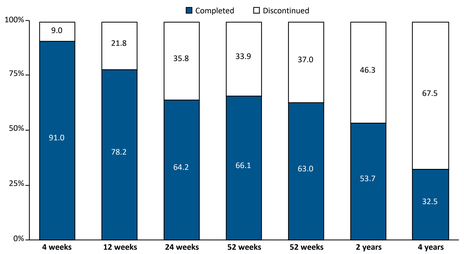
**Figure 9.** In an IPD meta-analysis across 3 clinical trials, OLZ/SAM was associated with significantly less weight gain and lower odds of CSWG vs olanzapine at 12 weeks of treatment, confirming consistent findings of weight mitigation




BD-I, bipolar I disorder; CSWG, clinically significant weight gain; IPD, individual patient data; LSM, least squares mean; LSMD, LSM difference; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

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

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



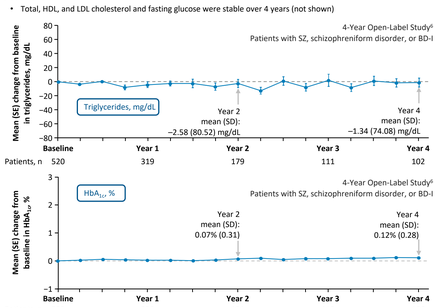

EXT, extension; OLZ/SAM, combined olanzapine/samidorphan.

## RESULTS (CON'T)

### Metabolic Effects

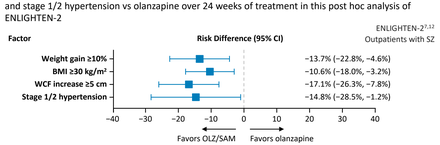
**Figure 11.** Changes in triglycerides and $HbA_{1c}$ were minimal following up to 4 years of OLZ/SAM open-label treatment

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




BD-I, bipolar I disorder; $HbA_{1c}$, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

**Figure 12.** OLZ/SAM treatment reduced the risk of developing CSWG, obesity, ≥5 cm WCF 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; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia; WCF, waist circumference.

## CONCLUSIONS

**Safety**
- The safety profile of OLZ/SAM was consistent with previous studies in the ENLIGHTEN program[3,5,7]

**Efficacy**
- The clinical symptom improvements observed in pivotal studies and associated open-label extensions[3-5,7,8] remained stable in the 4-year open-label extension study[6]
  - 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[6]
  - Negative symptoms of schizophrenia improved during short-term OLZ/SAM treatment, with continued improvement observed over 52 weeks of maintenance therapy[11]

**Weight and Metabolic Profile**
- OLZ/SAM treatment consistently resulted in significantly less weight gain vs olanzapine[5,7,9,10]; small changes in body weight and minimal changes in lipid/glycemic parameters were observed over long-term treatment[6]
  - 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[7,12]

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

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

Supported by funding from Alkermes, Inc.

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## DISCLOSURES

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***Key Contributors***

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the poster; gave final approval of the version to be presented; and agree to be accountable for all aspects of the work.

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