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

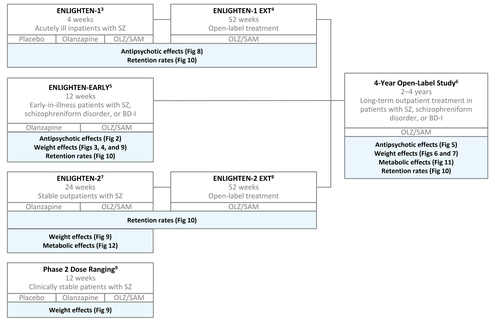
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BACKGROUND

- 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 • 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[3,7,9,10]	• Estimate of OLZ/SAM weight mitigation vs olanzapine at 12 weeks • Includes 3 phase 2/3 clinical trials with weight as primary/secondary outcome: – Phase 2 dose-ranging study – ENLIGHTEN-2 – ENLIGHTEN-EARLY
Negative symptoms of SZ[3,4,11]	• Post hoc, pooled analysis of ENLIGHTEN-1 and ENLIGHTEN-1 EXT • PANSS Total score and Positive, Negative, and General Psychopathology Subscale scores
Cardiometabolic risk factors[7,12]	• Post hoc analysis of ENLIGHTEN-2 • 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

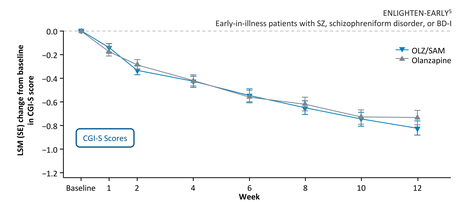
Most common AEs (≥5% of patients)[a,b]	All patients (N=523)
Weight increased	51 (9.8)
Headache	37 (7.1)
Anxiety	32 (6.1)
Insomnia	31 (5.9)
Somnolence	31 (5.9)
Nausea	30 (5.7)
Weight decreased	30 (5.7)

[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

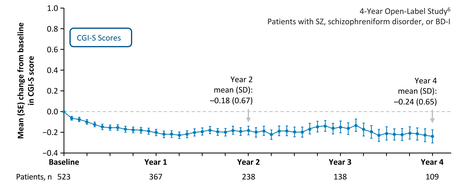
Antipsychotic Effects

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]



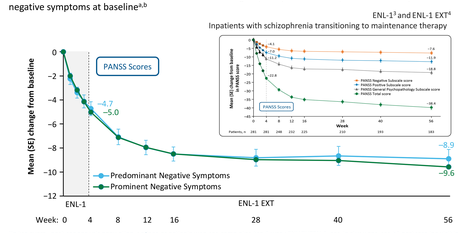
[a]Change from baseline to week 12 in CGI-S scores was a key secondary endpoint and was not formally tested due to early termination of the hierarchical testing procedure, which required statistical significance on the ≥10% weight gain endpoint before proceeding.
BD-I, bipolar I disorder; CGI-S, Clinical 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 *Mohr* Positive Symptoms Factor score ≤19 at baseline (PANSS *Mohr* Positive Factor: delusions [P1], hallucinatory behavior [P3], grandiosity [P5], suspiciousness/persecution [P6], and unusual thought content [G9]).
ENL-1, ENLIGHTEN-1; EXT, extension; 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.

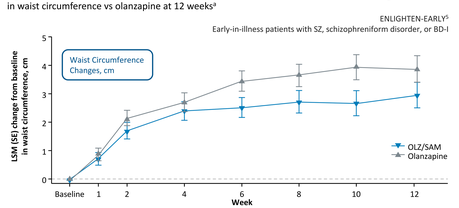
Figure 6. Small changes in body weight were observed for up to 4 years of OLZ/SAM open-label treatment[a]

[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 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

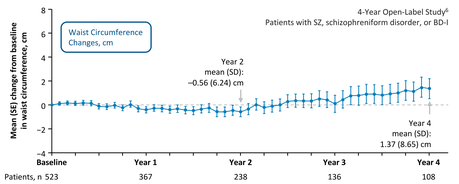
BD-I, bipolar I disorder; CSWG, clinically significant weight gain; IPD, individual patient data; LSM, least squares mean; LSMD, LSM difference; OLZ/SAM, combined olanzapine/samidorphan; SZ, schizophrenia.

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.

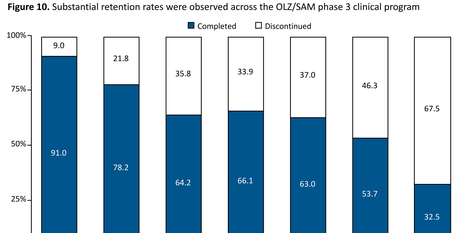
Figure 7. Minimal changes in waist circumference were observed for up to 4 years of OLZ/SAM treatment[a]



[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.

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



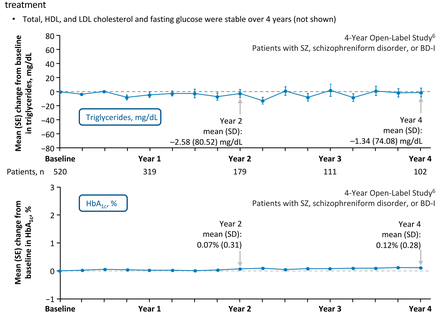
EXT, extension; OLZ/SAM, combined olanzapine/samidorphan.

RESULTS (cont'd)

Metabolic Effects

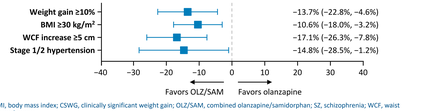
Figure 11. Changes in triglycerides and HbA_{1c} were minimal following up to 4 years of OLZ/SAM open-label treatment

- 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

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