Acute and Maintenance Treatment Effects of Olanzapine/Samidorphan on Negative Symptoms in Patients With Acute Schizophrenia: A Post Hoc Analysis

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INTRODUCTION

- Addressing negative symptoms in patients with schizophrenia is a treatment challenge
  - Negative symptoms of schizophrenia, including those related to reductions in motivation and interest (eg, avolition, anhedonia) or in expressive functions (eg, blunted affect, alogia), are associated with reduced functioning and are predictive of poor treatment response and functional outcomes[1]
- The combination of olanzapine and samidorphan (OLZ/SAM) is approved in the United States for the treatment of adults with schizophrenia[2]
- OLZ/SAM significantly reduced Positive and Negative Syndrome Scale[3] (PANSS) Total scores versus placebo in a randomized controlled study in patients with schizophrenia (ENLIGHTEN-1),[4] with continued improvement observed over 52 weeks of open-label treatment in an extension study (ENLIGHTEN-1 Extension)[5]
- The objective of this post hoc analysis was to evaluate the effect of acute and long-term treatment with OLZ/SAM on negative symptoms of schizophrenia

METHODS

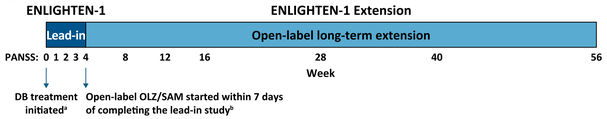
Patients

- Adult patients who completed a 4-week, olanzapine- and placebo-controlled study of OLZ/SAM for the treatment of acute schizophrenia[4] (ENLIGHTEN-1, lead-in study; NCT02634346) and had ≥1 postbaseline visit in a 52-week open-label extension study[5] (ENLIGHTEN-1 Extension, NCT02669758) were included in the post hoc analysis population (**Figure 1**)
- ENLIGHTEN-1 enrolled adult patients (18–70 years) experiencing an acute exacerbation or relapse of schizophrenia
  - Key inclusion criteria included PANSS Total score ≥80 at screening and baseline, and score ≥4 on 3 or 4 of the following symptoms: delusions (item P1), conceptual disorganization (P2), hallucinatory behavior (P3), and suspiciousness/persecution (P6)

Study Design and Assessments

- Because the analysis focused on long-term effects, data were integrated across ENLIGHTEN-1 and ENLIGHTEN-1 Extension, and ENLIGHTEN-1 treatment groups (week 1–4 data for the OLZ/SAM, placebo, and olanzapine treatment groups) were combined for this analysis (**Figure 1**)

Figure 1. Study Design



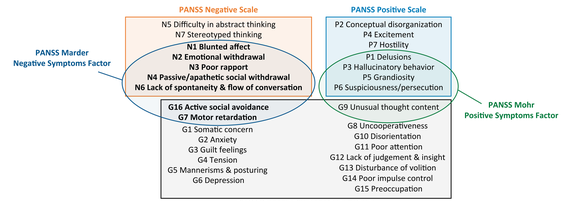
[a]Patients were randomized 1:1:1 to OLZ/SAM, olanzapine, or placebo. For patients in the olanzapine and OLZ/SAM treatment arms, the dose of olanzapine was 10 or 20 mg (target of 20 mg); the samidorphan dose was fixed at 10 mg. [b]Patients started on open-label OLZ/SAM 10/10 mg; dose could be increased to 15/10 or 20/10 mg during the first week of treatment or thereafter, based on investigator judgment.
DB, double-blind; OLZ/SAM, combination of olanzapine and samidorphan; PANSS, Positive and Negative Syndrome Scale.

- Negative symptoms were assessed based on PANSS Negative Symptoms Subscale[3] and Marder Negative Symptoms Factor[6] scores (**Figure 2**)
- Changes from baseline were evaluated for each postbaseline assessment, overall and among patients with high negative symptoms (PANSS Marder Negative Symptoms Factor score ≥24) at baseline
- To explore whether changes in negative symptoms were secondary to improvements in positive or other symptoms, a subgroup with high negative symptoms and low positive symptoms (PANSS Mohr Positive Symptoms Factor[7] score ≤19) at baseline was included

Statistical Analysis

- Changes from baseline in PANSS Total, PANSS Negative Symptoms Subscale, and Marder Negative Symptoms Factor scores were summarized descriptively; no formal statistical testing was conducted

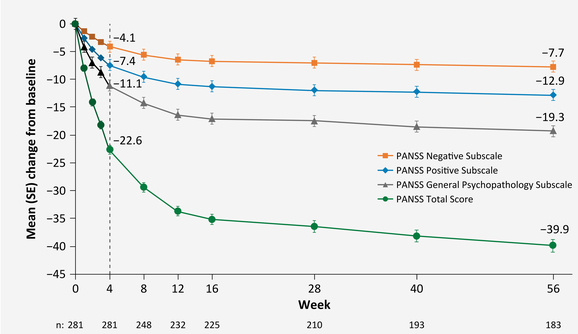
Figure 2. Item Composition of the PANSS Marder Negative Symptoms Factor and Mohr Positive Symptoms Factor[7,8]



PANSS, Positive and Negative Syndrome Scale.

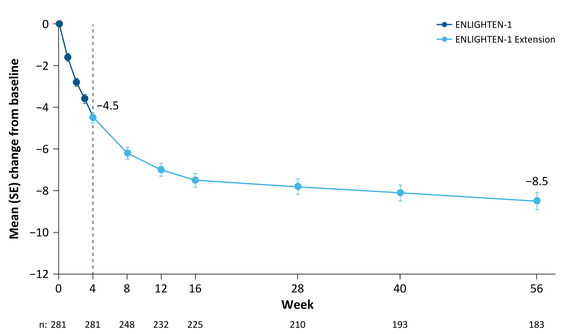
In this post hoc analysis, negative symptoms of schizophrenia decreased during short-term treatment and continued to decrease over 52 weeks of OLZ/SAM treatment, overall and among patients with high negative symptoms at baseline

Figure 3. Changes From Baseline in PANSS Total Score and PANSS Positive Subscale, Negative Subscale, and General Psychopathology Subscale Scores, Overall Post Hoc Analysis Population[a]



[a]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.
PANSS, Positive and Negative Syndrome Scale.

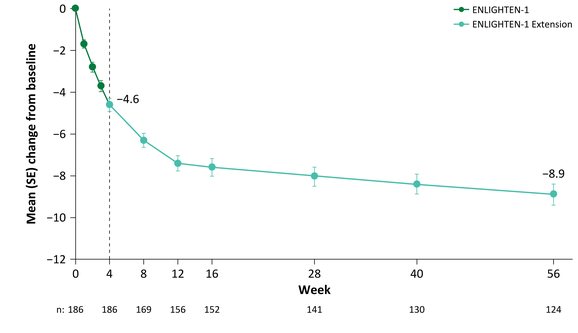
Figure 4. Changes From Baseline in PANSS Marder Negative Symptoms Factor[a] Score, Overall Post Hoc Analysis Population[b]



[a]Blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16). [b]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.
PANSS, Positive and Negative Syndrome Scale.

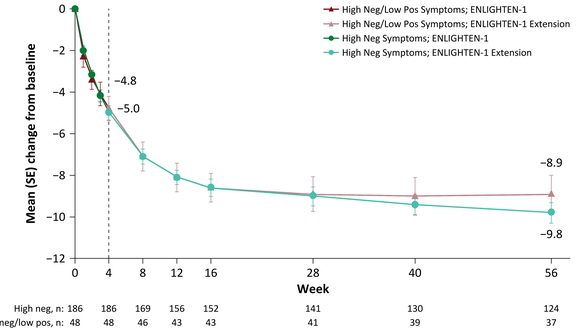
Subgroup Analyses

Figure 5. Changes From Baseline in PANSS Negative Symptoms Subscale[a] Score, High Baseline Negative Symptoms Subgroup[b]



[a]Blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), difficulty in abstract thinking (N5), lack of spontaneity/flow of conversation (N6), and stereotyped thinking (N7). [b]Patients with a PANSS Marder Negative Symptoms Factor score ≥24 at baseline.
PANSS, Positive and Negative Syndrome Scale.

Figure 6. Changes From Baseline in PANSS Marder Negative Symptoms Factor[a] Score, High Baseline Negative Symptoms[b] and High Negative/Low Positive Symptoms Subgroups[c]



[a]Blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16). [b]Patients with a PANSS Marder Negative Symptoms Factor score ≥24 at baseline. [c]Patients with a PANSS Marder Negative Symptoms Factor score ≥24 at baseline; a baseline score ≥4 on at least 2 of the following 3 PANSS items: blunted affect (N1), passive/apathetic social withdrawal (N4), or lack of spontaneity/flow of conversation (N6); and a PANSS Mohr Positive Symptoms Factor score ≤19 at baseline. Mohr Positive Symptoms Factor: delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), and unusual thought content (G9).[7]
Neg, negative; PANSS, Positive and Negative Syndrome Scale; pos, positive.

Patients

Table 1. Demographics and ENLIGHTEN-1 Study Baseline Clinical Characteristics, Post Hoc Analysis Population[a]

Characteristics	All Patients (N=281)
Age, mean (SD), years	41.7 (11.6)
Sex, male, n (%)	160 (56.9)
Race, n (%)	
White	221 (78.6)
Black or African American	53 (18.9)
Asian	3 (1.1)
Other	4 (1.4)
BMI, mean (SD), kg/m^2	26.2 (4.9)
CGI-S score, mean (SD)	5.1 (0.7)
PANSS Total score, mean (SD)	101.7 (11.1)
PANSS Marder Negative Symptoms Factor[b] score, mean (SD)	25.2 (4.6)

[a]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. [b]PANSS Marder Negative Symptoms Factor: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16).
BMI, body mass index; CGI-S, Clinical Global Impressions–Severity; PANSS, Positive and Negative Syndrome Scale.

LIMITATIONS

- The lack of a comparator in the ENLIGHTEN-1 Extension limits interpretation of the results
- The post hoc nature of this analysis of negative symptoms of schizophrenia limits interpretation of the results
- Treatment groups in the placebo-controlled 4-week study were combined in this analysis
- The number of patients who met the criteria for high negative symptoms and low positive symptoms at baseline was small
- Because the patients met specified enrollment criteria for ENLIGHTEN-1, results from this analysis may not be generalizable to the real-world population of patients with schizophrenia who are started on antipsychotic treatment

CONCLUSIONS

- In this post hoc analysis, negative symptoms of schizophrenia decreased during short-term treatment, and continued improvement was observed over 52 weeks of maintenance therapy with OLZ/SAM
- Improvement in negative symptoms was observed overall and among patients with high negative symptoms at baseline
- Improvement was similar for patients with high negative symptoms at baseline and those with high negative/low positive symptoms
- The clinical relevance of the observed improvement in negative symptom scores could not be determined directly because functional outcome assessments were not included in ENLIGHTEN-1 and the ENLIGHTEN-1 Extension
  - However, the 9-point change in PANSS Negative Symptoms Subscale score in the high negative symptoms subgroup is similar to clinically relevant reductions reported previously[9]

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AUTHOR DISCLOSURES

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