Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia:
Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study

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ABSTRACT

Objective: To assess the antipsychotic efficacy and safety of a combination of olanzapine and samidorphan (OLZ/SAM).

Methods: This 4-week, phase 3, randomized, double-blind, placebo- and olanzapine-controlled study was conducted from December 2015 to June 2017 in adults with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria who were experiencing an acute exacerbation. Patients were randomized 1:1:1 to OLZ/SAM, olanzapine monotherapy, or placebo. The primary and key secondary efficacy endpoint assessed was the change in Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impressions–Severity of Illness Scale (CGI-S) score between baseline and week 4, respectively, for OLZ/SAM versus placebo. Safety monitoring occurred throughout.

Results: 401 patients received ≥ 1 dose of study drug; 352 completed treatment. Treatment with OLZ/SAM resulted in significant improvements versus placebo in PANSS total and CGI-S scores from baseline to week 4 (least squares [LS] mean ± SE: −6.4 ± 1.8 [$P < .001$] and −0.38 ± 0.12 [$P = .002$], respectively). Olanzapine treatment resulted in similar improvements (PANSS and CGI-S LS mean ± SE of −5.3 ± 1.84 [$P = .004$] and −0.44 ± 0.12 [$P < .001$], respectively). Adverse events (AEs) occurred in 54.5%, 54.9%, and 44.8% of patients on OLZ/SAM, olanzapine, and placebo, respectively. Weight gain, somnolence, dry mouth, anxiety, and headache were the most common AEs (ie, ≥ 5%) with active treatment.

Conclusions: OLZ/SAM treatment resulted in statistically and clinically significant efficacy improvements over 4 weeks versus placebo in adults with acutely exacerbated schizophrenia. Improvements were similar to those observed with olanzapine. OLZ/SAM was well tolerated, with a safety profile similar to that of olanzapine.

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Olanzapine is one of the most efficacious antipsychotic agents available for the treatment of schizophrenia.[1–4] Its success is exemplified in long-term studies,[2–4] in which rates of all-cause discontinuation and discontinuation due to lack of efficacy were lower for patients on olanzapine than other antipsychotics. However, significant safety concerns regarding weight gain and associated metabolic dysregulation have limited the clinical use of olanzapine.[5,6] To date, there have been no approved pharmacologic interventions that fundamentally change the benefit-risk profile of olanzapine.[7–9]

The underlying mechanisms of antipsychotic-induced weight gain and associated metabolic derangements are not understood. Past research has implicated antipsychotic medication effects at serotonin (5-HT)–2C,[10] H_1,[11] and M_3-muscarinic[12] receptors, as well as increases in leptin levels,[13] among others, as potential causes. As a result, various strategies have been employed to reverse or prevent such effects. A 2010 meta-analysis[9] of 32 studies investigating 15 different pharmacologic interventions found that metformin, fenfluramine, sibutramine, topiramate, and reboxetine provided statistically significantly greater weight loss versus placebo, although the risk reduction was modest and the evidence inadequate to recommend broad use of any specific intervention.

Preclinical evidence suggests a critical role for the opioid system in modulating feeding behavior and metabolism. For example, decrease in weight gain has been reported in μ-, κ-, and δ-opioid receptor knockout mice despite no differences in caloric intake in μ- and κ-opioid receptor knockout mice compared with wild-type mice.[14–16] Therefore, adding an opioid antagonist to a central nervous system–active drug known to cause weight gain such as olanzapine may mitigate weight gain and associated metabolic dysregulation from olanzapine use. Samidorphan is a new molecular entity that, in vitro, binds with high affinity to human μ-, κ-, and δ-opioid receptors and acts as an antagonist at μ-opioid receptors and partial agonist at κ- and δ-opioid receptors.[17,18] In vivo, samidorphan has been demonstrated to function as an opioid receptor antagonist.[19] The combination of olanzapine and samidorphan (OLZ/SAM) is intended to provide the antipsychotic efficacy of olanzapine while mitigating weight gain associated with olanzapine;

Clinical Points

- ENLIGHTEN-1 is a phase 3 study that evaluated OLZ/SAM, a combination of olanzapine and the opioid antagonist samidorphan, versus placebo in patients with an acute schizophrenia exacerbation; an olanzapine arm was included for assay sensitivity.

- PANSS total and CGI-S score reductions with OLZ/SAM were significant versus placebo and similar to those with olanzapine versus placebo.

- If approved for use, OLZ/SAM may be an option for patients experiencing an acute exacerbation of schizophrenia; it appears to retain the antipsychotic efficacy of olanzapine with the added benefit of mitigated weight gain, which would support long-term treatment.

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samidorphan does not bind to any receptors other than μ-, κ-, or δ-opioid receptors[18] and, as such, would not be expected to have antipsychotic properties. In a phase 1 study in healthy volunteers, weight gain was significantly lower in those treated with OLZ/SAM than those treated with olanzapine monotherapy.[20] In a subsequent phase 2 study[21] in patients with schizophrenia who were clinically stable (defined as a Positive and Negative Syndrome Scale [PANSS] score ≤ 80 and a Clinical Global Impressions–Severity of Illness Scale [CGI-S] score ≤ 3 at screening), the antipsychotic efficacy of OLZ/SAM was similar to that of olanzapine; the presence of samidorphan mitigated olanzapine-associated weight gain, although a difference in weight gain was not observed until after 4 weeks of treatment.

Here, we report findings from a phase 3 study evaluating the antipsychotic efficacy and safety of OLZ/SAM compared with placebo in patients with an acute exacerbation of schizophrenia, a more severely ill patient group than that studied in phase 2. The study was performed to determine if the antipsychotic efficacy of olanzapine would be adversely affected by the addition of samidorphan. An olanzapine active control arm was also included to confirm validity of the study.

METHODS

This multicenter study (ClinicalTrials.gov identifier: NCT02634346; European Union Drug Regulating Authority Clinical Trials [EudraCT] Database number: 2015-003373-15) was conducted in the United States and Europe from December 2015 to June 2017 and in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. The study protocols, amendments, and informed consent forms were approved by an independent ethics committee/institutional review board for each site. All patients provided written informed consent before entering the study.

Study Design and Treatments

This was a 4-week, phase 3, double-blind, randomized, active- (olanzapine) and placebo-controlled study of OLZ/SAM in patients experiencing an acute exacerbation of schizophrenia. The study consisted of a screening phase of up to 10 days (Visit 1) during which prior antipsychotic treatment was discontinued, a 4-week treatment period (Visits 2–6) that included 2 weeks of inpatient treatment (dose titration permitted) followed by 2 weeks of inpatient/outpatient treatment (fixed dose), and a follow-up (Visit 7) on day 43 (Figure 1). OLZ/SAM, olanzapine, or placebo was administered as a single, coated bilayer tablet. For patients in the active treatment arms (olanzapine and OLZ/SAM), the dose of olanzapine was 10 or 20 mg (target of 20 mg). For patients in the OLZ/SAM group, the samidorphan dose was fixed at 10 mg, based on a previous phase 2 study in which 10 mg of samidorphan added to olanzapine provided significant mitigation of weight gain that was numerically greater than that observed with 5 mg of samidorphan, and comparable to that with 20 mg of samidorphan with a better safety profile.[21]

Patients were randomized 1:1:1 to OLZ/SAM, olanzapine, or placebo administered orally, once daily for up to 4 weeks. As the enrolled patients were acutely psychotic upon study entry and current treatments were not working, ongoing antipsychotic medications were stopped at Visit 2 (randomization), and treatment with study medication commenced immediately. There was no tapering of prior antipsychotic medication. On days 1 and 2, patients randomized to OLZ/SAM received 10 mg/10 mg, and patients randomized to olanzapine received 10 mg. On day 3, the dose was increased to 20 mg/10 mg for the OLZ/SAM group and 20 mg for the olanzapine group. At the end of week 1, doses could be decreased for tolerability to 10 mg of olanzapine at the discretion of the investigator. Thereafter, no dose adjustments were permitted from weeks 2 to 4. All clinical staff, patients, and caregivers were blinded to treatment assignment until database lock.

Patients were required to be inpatients for the first 2 weeks of the treatment period, and those who met the criteria for discharge could then complete the remaining 2 weeks on either an inpatient or outpatient basis. However, patients were encouraged to remain as inpatients for all 4 weeks.

Patients who completed the full 4-week treatment period were eligible for a 52-week, open-label, long-term safety extension study. If patients discontinued early or did not enter the long-term safety study, they were monitored for 2 weeks of safety follow-up after the last dose of treatment.

Patients

Patients included in the study were adults aged 18 to 70 years with a *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*),[22] diagnosis of schizophrenia who met criteria for an acute exacerbation or relapse of schizophrenia symptoms, a PANSS[23] score ≥ 80 with a score ≥ 4 on at least 3 of the following items from the PANSS: Item 1, delusions; Item 2, conceptual disorganization; Item 3, hallucinatory behavior; and Item 6, suspiciousness/persecution, and a CGI-S[24] score ≥ 4 at baseline and screening. Patients were required to have a body mass index (BMI) of 18.0 to 40.0 kg/m² and to abide by contraception

Figure 1. Study Design
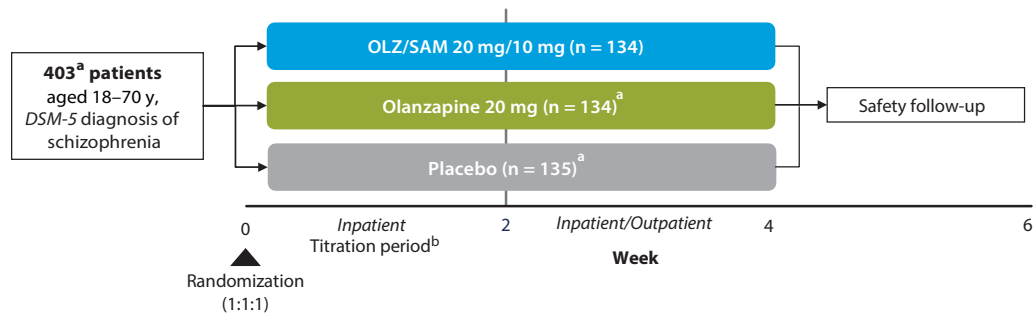
[a]Two patients (olanzapine, n = 1; placebo, n = 1) withdrew prior to receiving study drug.
[b]On days 1 and 2, patients randomized to OLZ/SAM received 10 mg/10 mg and patients randomized to olanzapine received 10 mg. On day 3, the dose was increased to 20 mg/10 mg for the OLZ/SAM group and 20 mg for the olanzapine group. At the end of week 1, doses could be decreased to 10 mg of olanzapine at the discretion of the investigator for tolerability. No dose adjustments were permitted from weeks 2 to 4.
Abbreviations: DSM-5 = Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition; OLZ/SAM = olanzapine/samidorphan.

methods stipulated in the protocol. Key exclusion criteria included the presence of a clinically significant or unstable medical illness, condition, or disorder that could potentially compromise patient safety; a history of diabetes; moderate or severe alcohol or drug use disorder currently or during the 3 months prior to screening; a positive urine drug screen for opioids, amphetamine/methamphetamine, phencyclidine, or cocaine at screening; or an assessment that the patient was at risk for suicide. Previous exposure to olanzapine, mesoridazine, chlorpromazine, thioridazine, or a long-acting injectable antipsychotic medication within 6 months prior to screening (with the exception of those receiving 3-month paliperidone, which must not have been received within 12 months of screening) was also exclusionary. Patients were excluded if they initiated first antipsychotic treatment within the past 12 months, < 1 year had elapsed since the initial onset of active-phase of schizophrenia symptoms, or they received clozapine within 6 months prior to screening. Patients with a history of clozapine use for treatment-resistant schizophrenia or an inadequate response to treatment with olanzapine were also excluded. Patients taking opioid agonists within 14 days, or opioid antagonists within 60 days, prior to screening were not allowed to participate. Likewise, the use of weight-loss drugs or hypoglycemic agents at screening, or the use of statins, if initiated or the dose changed within 3 months, was exclusionary.

In general, the use of any psychotropic medications (monoamine oxidase inhibitors, oral or long-acting formulations of antipsychotic agents, nicotine replacement therapy, over-the-counter medications for weight loss, systemic steroids, topiramate or combinations thereof, antidepressants, strong inducers/inhibitors of cytochrome P450 3A4 started within 30 days, or opioid agonists started within 14 days of screening) was prohibited. Exceptions were the use of β-blockers, antihistamines, and anticholinergics for the treatment of akathisia and anticholinergics and benzodiazepines (≤ 2 mg/d of lorazepam) for the treatment of extrapyramidal symptoms.

Study Assessments

The primary endpoint was change from baseline in PANSS total score at week 4. The key secondary endpoint was change from baseline in CGI-S score at week 4. Other endpoints included change from baseline in scores on PANSS subscales (positive, negative, and general psychopathology), the proportion of PANSS responders (defined as ≥ 30% improvement from baseline in PANSS total score), and the proportion of Clinical Global Impressions–Improvement Scale (CGI-I) responders (defined as a CGI-I score of ≤ 2 [2 = much improved, 1 = very much improved]).
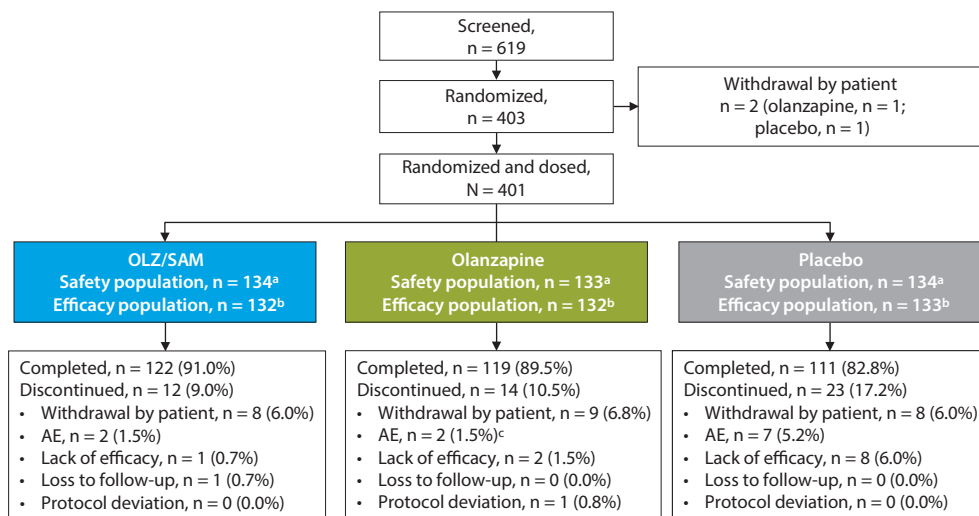
Subgroup analyses of the primary endpoint were performed for each of the following subgroups: sex (male, female), age (< 55 years, ≥ 55 years), race (white, black, other), and baseline PANSS total score (< 95 points, ≥ 95 points).

Safety evaluations included assessment of adverse events (AEs); ratings of extrapyramidal symptoms using the Abnormal Involuntary Movement Scale (AIMS),[25] the Barnes Akathisia Rating Scale (BARS),[26] and the Simpson-Angus Scale (SAS)[27]; the Columbia–Suicide Severity Rating Scale (C-SSRS)[28,29]; clinical laboratory assessments (chemistry, hematology, and urinalysis); and electrocardiograms. Height, weight, and waist circumference measurements and a full physical examination were performed at screening. Weight and waist circumference measurements and a brief physical examination were performed at Visits 2, 6, and 7.

Statistical Analysis

The efficacy population included all randomized patients who received at least 1 dose of study drug and had at least 1 postbaseline PANSS assessment. The continuous efficacy endpoints were analyzed using a mixed model with repeated measures (MMRM) with an unstructured variance-covariance matrix. The model included region (US vs non-US), visit, treatment, and the interaction of term-of-visit and treatment as categorical variables, and baseline scores as a covariate. The Kenward-Roger approximation was used to adjust the denominator degree of freedom. The least squares (LS) mean ± SE change from baseline

Figure 2. Patient Disposition

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                              ┌─────────────┐
                              │  Screened,  │
                              │   n = 619   │
                              └──────┬──────┘
                                     │
                              ┌──────┴──────┐      ┌──────────────────────────┐
                              │ Randomized, ├─────▶│  Withdrawal by patient   │
                              │   n = 403   │      │ n = 2 (olanzapine, n = 1;│
                              └──────┬──────┘      │     placebo, n = 1)      │
                                     │             └──────────────────────────┘
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                          │ Randomized and dosed,│
                          │      N = 401         │
                          └──────────┬──────────┘
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OLZ/SAM	Olanzapine	Placebo
Safety population, n = 134[a]	**Safety population, n = 133[a]**	**Safety population, n = 134[a]**
Efficacy population, n = 132[b]	**Efficacy population, n = 132[b]**	**Efficacy population, n = 133[b]**
Completed, n = 122 (91.0%)	Completed, n = 119 (89.5%)	Completed, n = 111 (82.8%)
Discontinued, n = 12 (9.0%)	Discontinued, n = 14 (10.5%)	Discontinued, n = 23 (17.2%)
• Withdrawal by patient, n = 8 (6.0%)	• Withdrawal by patient, n = 9 (6.8%)	• Withdrawal by patient, n = 8 (6.0%)
• AE, n = 2 (1.5%)	• AE, n = 2 (1.5%)[c]	• AE, n = 7 (5.2%)
• Lack of efficacy, n = 1 (0.7%)	• Lack of efficacy, n = 2 (1.5%)	• Lack of efficacy, n = 8 (6.0%)
• Loss to follow-up, n = 1 (0.7%)	• Loss to follow-up, n = 0 (0.0%)	• Loss to follow-up, n = 0 (0.0%)
• Protocol deviation, n = 0 (0.0%)	• Protocol deviation, n = 1 (0.8%)	• Protocol deviation, n = 0 (0.0%)

[a]Safety population included all randomized patients who received at least 1 dose of study drug during the double-blind treatment period.
[b]The efficacy population included all patients in the safety population who had at least 1 post-baseline PANSS assessment.
[c]One additional patient died 2 days after the final dose of study drug, and the death was considered a discontinuation due to an AE.
Abbreviations: AE = adverse event, OLZ/SAM = olanzapine/samidorphan, PANSS = Positive and Negative Syndrome Scale.

for each treatment group was reported, as were the LS mean ± SE difference and 95% CI for the active treatment groups (OLZ/SAM and olanzapine) versus placebo. Binary efficacy endpoints were analyzed using a logistic regression model based on last-observation-carried-forward imputation for missing data. The model included the region and treatment group as factors and baseline scores as covariates. The prespecified comparison was between the placebo and OLZ/SAM groups and between the placebo and olanzapine groups; comparisons of the olanzapine and OLZ/SAM groups were performed post hoc.

Safety was assessed in all randomized patients who received at least 1 dose of the study drug. Safety and tolerability were analyzed using descriptive statistics based on observed data.

The sample size calculation was performed based on *t* test with the following assumptions: a 10-point improvement of PANSS total score at week 4 of OLZ/SAM relative to placebo, a standard deviation (SD) of 20, and a dropout rate of 30%. The planned sample size was 390 patients (130 per treatment group). This sample size would provide at least 90% power to show superiority of the OLZ/SAM group compared with the placebo group at a 2-sided α level of .05.

RESULTS

Patient Disposition and Baseline Characteristics

Of 403 randomized patients, 2 (1 in the olanzapine group and 1 in the placebo group) withdrew from the study prior to receiving study drug. Overall, 87.8%

Table 1. Baseline Demographics and Characteristics (safety population)

Characteristic	OLZ/SAM[a] n = 134	Olanzapine[a] n = 133	Placebo n = 134	All Patients N = 401
Age, mean ± SD, y	40.8 ± 12.6	41.5 ± 10.9	41.1 ± 10.6	41.1 ± 11.4
Male, n (%)	85 (63.4)	81 (60.9)	78 (58.2)	244 (60.8)
Race, n (%)				
White	87 (64.9)	99 (74.4)	91 (67.9)	277 (69.1)
Black	42 (31.3)	33 (24.8)	38 (28.4)	113 (28.2)
Asian	1 (0.7)	0	3 (2.2)	4 (1.0)
Other	4 (3.0)	1 (0.8)	2 (1.5)	7 (1.7)
Region, US, n (%)	55 (41.0)	50 (37.6)	49 (36.6)	154 (38.4)
Weight, mean ± SD, kg	77.9 ± 15.4	82.2 ± 19.3	76.6 ± 15.9	78.9 ± 17.1
BMI, mean ± SD, kg/m²	26.3 ± 4.5	27.5 ± 5.4	25.9 ± 4.8	26.6 ± 4.9
Obese (≥ 30 kg/m²), n (%)	28 (20.9)	46 (34.6)	30 (22.4)	104 (25.9)

[a]The average of mean olanzapine dose was 18.4 mg/d in both active treatment arms.
Abbreviations: BMI = body mass index, OLZ/SAM = olanzapine/samidorphan.

(n = 352) of patients completed the double-blind treatment period (91.0% [n = 122] in the OLZ/SAM group, 89.5% [n = 119] in the olanzapine group, and 82.8% [n = 111] in the placebo group); 12.2% (n = 49) of patients discontinued the double-blind treatment period early (Figure 2). The most common reasons for treatment discontinuation were withdrawal by patient (n = 25; 6.2%), AE (n = 11; 2.7%), and lack of efficacy (n = 11; 2.7%).

In general, baseline characteristics were similar between groups. Overall, the mean ± SD age of patients was 41.1 ± 11.4 years, 244 (60.8%) were male, 113 (28.2%) were black, and 154 (38.4%) were in the United States (Table 1). Mean baseline weight and BMI were higher in the olanzapine group (82.2 kg and 27.5 kg/m²) compared with the OLZ/SAM (77.9 kg and 26.3 kg/m²) and placebo groups (76.6 kg and 25.9 kg/m²). The OLZ/SAM group had a higher percentage of black patients (n = 42, 31.3%) than the placebo (n = 38, 28.4%) or the olanzapine groups (n = 33, 24.8%).

Figure 3. Change From Baseline in (A) PANSS Total Score and (B) CGI-S Score by Week (MMRM; efficacy population)[a,b]

A. PANSS Total Score
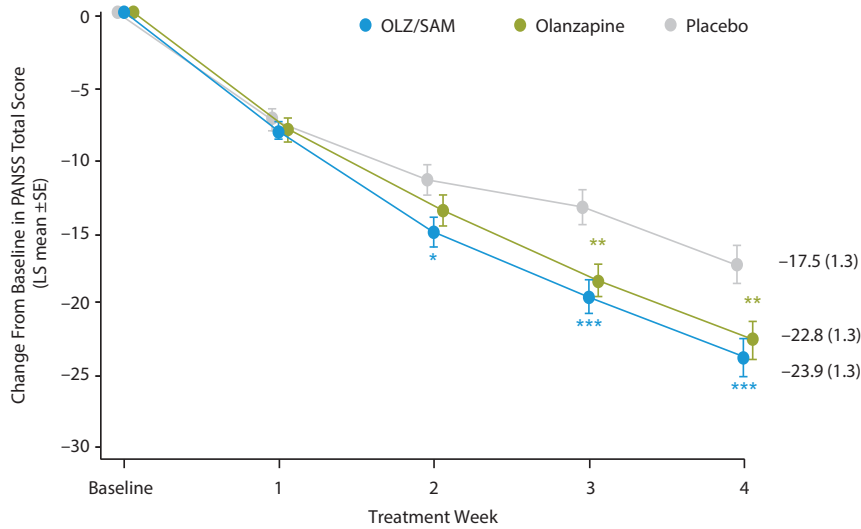
Score	OLZ/SAM	Olanzapine	Placebo
PANSS total score at baseline	n = 132	n = 132	n = 133
Mean ± SD	101.8 ± 11.6	100.6 ± 12.1	102.7 ± 11.9
Change from baseline at wk 4 in PANSS total score	n = 124	n = 120	n = 112
Mean ± SD	−23.7 ± 12.6	−22.4 ± 13.6	−19.4 ± 14.8
LS mean ± SE	−23.9 ± 1.3	−22.8 ± 1.3	−17.5 ± 1.3
LS mean difference ± SE vs placebo	−6.4 ± 1.8	−5.3 ± 1.8	…
P value vs placebo	<.001	.004	…

B. CGI-S Score
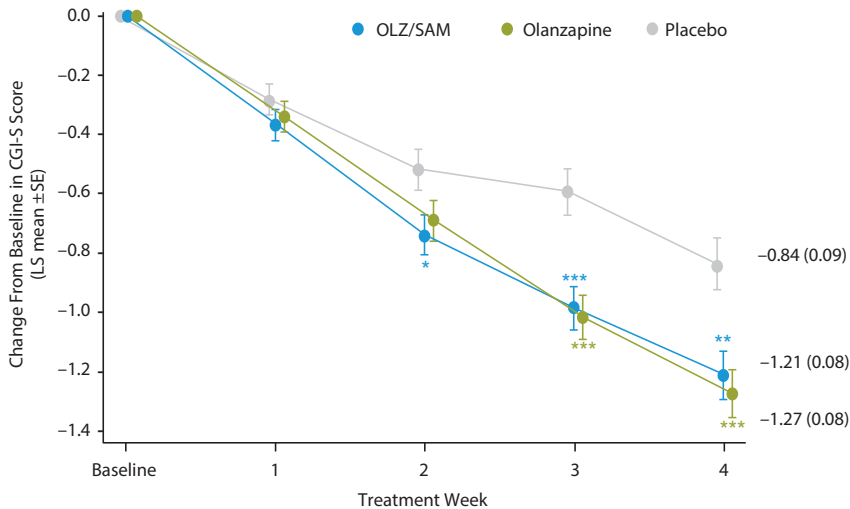
Score	OLZ/SAM	Olanzapine	Placebo
CGI-S score at baseline	n = 132	n = 132	n = 133
Mean ± SD	5.1 ± 0.7	5.1 ± 0.7	5.1 ± 0.7
Change from baseline at wk 4 in CGI-S total score	n = 124	n = 120	n = 112
Mean ± SD	−1.2 ± 0.9	−1.3 ± 1.0	−0.9 ± 1.0
LS mean ± SE	−1.2 ± 1.0	−1.3 ± 1.0	−0.8 ± 1.0
LS mean difference ± SE vs placebo	−0.4 ± 0.1	−0.4 ± 0.1	…
P value vs placebo	.002	<.001	…

[a]Mixed model repeated measures; efficacy population.
[b]The average of mean olanzapine dose was 18.4 mg/d in both the OLZ/SAM and olanzapine groups.
*P < .05; **P < .01; ***P < .001 (all vs placebo).
Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness Scale, LS = least squares, OLZ/SAM = olanzapine/samidorphan, PANSS = Postitive and Negative Syndrome Scale.

Table 2. Summary of AEs and Extrapyramidal Symptoms During the Double-Blind Treatment Phase (safety population)[a]

Category	OLZ/SAM n = 134	Olanzapine n = 133	Placebo n = 134
Any AE	73 (54.5)	73 (54.9)	60 (44.8)
Serious AEs	1 (0.7)	1 (0.8)	0
AEs leading to discontinuation	2 (1.5)	3 (2.3)	7 (5.2)
Death	0	1 (0.8)	0
AEs in ≥ 5% of patients in any group			
Weight increased[b]	25 (18.7)	19 (14.3)	4 (3.0)
Somnolence	12 (9.0)	13 (9.8)	3 (2.2)
Dry mouth	10 (7.5)	7 (5.3)	1 (0.7)
Anxiety	8 (6.0)	7 (5.3)	8 (6.0)
Headache	8 (6.0)	7 (5.3)	4 (3.0)
Schizophrenia exacerbation/worsening[c]	1 (0.7)	2 (1.5)	8 (6.0)
Extrapyramidal symptoms based on movement disorder scale cutoff scores[d]			
Parkinsonism[e]	5 (3.7)	6 (4.5)	14 (10.4)
Akathisia[f]	8 (6.0)	6 (4.5)	11 (8.2)
Dyskinesia[g]	2 (1.5)	1 (0.8)	2 (1.5)

[a]Values are shown as n (%).
[b]An AE of weight increased was recorded if, in the opinion of the investigator, weight gain was felt to be clinically significant.
[c]Schizophrenia exacerbation or worsening (preferred term: *schizophrenia*) was defined according to the *Medical Dictionary for Regulatory Activities* (version 19.0).
[d]Includes double-blind treatment period and follow-up period.
[e]Simpson-Angus Scale total score > 3.
[f]Barnes Akathisia Rating Scale global clinical assessment score ≥ 2.
[g]Abnormal Involuntary Movement Scale score ≥ 3 on any of the first 7 items or a score ≥ 2 on 2 or more of any of the first 7 items.
Abbreviations: AE = adverse event, OLZ/SAM = olanzapine/samidorphan.

A higher proportion of obese (BMI ≥ 30 kg/m^2) patients were in the olanzapine group (n = 46, 34.6%) compared with the OLZ/SAM (n = 28, 20.9%) and placebo (n = 30, 22.4%) groups. Overall, 357 patients (89.0%) had taken at least 1 antipsychotic prior to study entry; the most common were risperidone (n = 124, 30.9%) and haloperidol (n = 122, 30.4%; Supplementary Table 1).

The mean olanzapine dose was 18.4 mg/d in both active treatment arms, and the mean modal dose of olanzapine was 19.0 mg/d for the OLZ/SAM group and 18.9 mg/d for the olanzapine group. The majority of patients in both the OLZ/SAM (n = 119, 88.8%) and olanzapine (n = 119, 89.5%) groups received olanzapine 20 mg as the final dose of study drug. Approximately 85% remained as inpatients for the full duration of the study.

Efficacy

The LS mean difference ± SE versus placebo in change from baseline at week 4 in PANSS total score was −6.4 ± 1.8 (*P* < .001) for the OLZ/SAM group and −5.3 ± 1.8 (*P* = .004) for the olanzapine group (Figure 3A). A statistically significant LS mean difference from placebo in the OLZ/SAM group was observed from week 2 onward.

The LS mean difference ± SE versus placebo in change from baseline at week 4 in the OLZ/SAM and olanzapine groups was −1.9 ± 0.6 and −1.8 ± 0.6, respectively, for the PANSS positive subscale; −1.0 ± 0.5 and −0.5 ± 0.5, respectively, for the PANSS negative subscale; and −3.4 ± 0.9 and −2.8 ± 0.9, respectively, for the PANSS general psychopathology subscale (Supplementary Figure 1). The proportion of PANSS responders at week 4 was significantly greater for OLZ/SAM (n = 79, 59.8%; *P* < .001) and olanzapine (n = 71, 53.8%; *P* = .015) compared with placebo (n = 51, 38.3%; Supplementary Figure 2A).

The LS mean difference ± SE versus placebo in change from baseline at week 4 in CGI-S score was −0.38 ± 0.12 (*P* = .002) for the OLZ/SAM group and −0.44 ± 0.12 (*P* < .001) for the olanzapine group (Figure 3B). Compared with placebo (n = 44, 33.1%), the proportion of CGI-I responders at week 4 was significantly greater for OLZ/SAM (n = 76, 57.6%; *P* < .001) and olanzapine (n = 67, 50.8%; *P* = .004; Supplementary Figure 2B).

Subgroup analyses. The efficacy of OLZ/SAM versus placebo, as assessed by change from baseline at week 4 in PANSS total score, was similar to olanzapine versus placebo overall and in each subgroup of interest (age: < 55 or ≥ 55 years; sex: male or female; race: white, black, or other; and PANSS total score: < 95 vs ≥ 95; Supplementary Figure 3A). The efficacy of OLZ/SAM was also similar to olanzapine overall and in each subgroup of interest (Supplementary Figure 3B).

Safety

Adverse events. Overall, 206 patients (51.4%) experienced ≥ 1 AE: 73 (54.5%) treated with OLZ/SAM, 73 (54.9%) with olanzapine, and 60 (44.8%) with placebo. Most AEs were mild or moderate in severity. AEs reported in ≥ 5% of patients in any treatment group are summarized in Table 2. AEs reported in ≥ 5% of patients in the OLZ/SAM group and that occurred at a rate of at least 2-fold greater than in placebo group were weight gain, somnolence, dry mouth, and headache (Table 2). The mean ± SD change in weight from baseline to week 4 in the placebo group was 0.24 ± 2.76 kg compared with 3.02 ± 3.56 kg for OLZ/SAM and 2.38 ± 3.65 kg in the olanzapine group.

Overall, 12 patients (3.0%) discontinued treatment because of AEs. The percentage of patients who discontinued treatment owing to AEs was 1.5% (2/134) in the OLZ/SAM group, 2.3% (3/133) in the olanzapine group, and 5.2% (7/134) in the placebo group (Table 2). Of the AEs leading to study drug discontinuation, alanine aminotransferase increase (OLZ/SAM group), hyperglycemia (olanzapine group), worsening of schizophrenia (placebo group), and seizure (placebo group) were considered by the investigator to be probably or definitely related to study drug. One death was reported during the study. A patient taking olanzapine died from heroin overdose 2 days after completing study treatment; this was considered a serious AE. The patient had not expressed any suicidal ideation upon completion of the study. A different patient in the OLZ/SAM group experienced a serious AE of catatonia 2 days after discontinuing the study drug. Neither event was considered by the investigator to be related to the study drug.

Abnormal movements. Mean changes from baseline during the double-blind treatment period were small and clinically insignificant as assessed by the AIMS, BARS, and SAS, with no notable differences between

treatment groups (Supplementary Table 2); dyskinesia was not reported as an AE for any patient during the study.

In the double-blind treatment and follow-up periods, rates of extrapyramidal symptoms defined by specific cutoff scores (ie, SAS total score > 3; BARS global clinical assessment score ≥ 2; AIMS score ≥ 3 on any of the first 7 items or a score of ≥ 2 on 2 or more of any of the first 7 items) are presented in Table 2. The proportion of patients who experienced parkinsonism was lower in the OLZ/SAM and olanzapine groups compared with the placebo group, and the rates of akathisia and dyskinesia were comparable across all 3 groups based on this analysis.

Columbia–Suicide Severity Rating Scale. Suicidal ideation was reported in 2 patients (1.5%) in the olanzapine group and 3 patients (2.2%) in the placebo group; no patients in the OLZ/SAM group reported suicidal ideation. No patient in any treatment group exhibited suicidal behavior or nonsuicidal self-injurious behavior at any time during the study.

DISCUSSION

Key goals in the treatment of patients with an acute exacerbation of schizophrenia are to rapidly control symptoms, such as aggression and agitation, and return the patient to the best level of functioning possible.[30] In this study, treatment with OLZ/SAM, when compared with placebo, resulted in significant (*P* < .001) improvements in the primary endpoint, change from baseline in PANSS total score at week 4, in patients with an acute exacerbation of schizophrenia, a population with more severe schizophrenia symptoms than the population of the previous phase 2 study. Statistically significant improvements were observed as early as week 2 in the OLZ/SAM group (*P* = .015) compared with the placebo group and were maintained through week 4. Treatment with olanzapine also resulted in similar statistically significant improvements compared with placebo, confirming the study's validity. The reductions in PANSS total scores for patients on active treatment were similar in magnitude to those previously reported[31–33] in patients treated with olanzapine for an acute exacerbation of schizophrenia. In this study, the time course and effect size of the response for the 2 active medications, olanzapine and OLZ/SAM, were similar. These findings demonstrate that samidorphan does not have an impact on the antipsychotic efficacy of olanzapine. Post hoc analyses indicated that the efficacy of OLZ/SAM was similar to that of olanzapine.

The efficacy of OLZ/SAM was further supported by significant (*P* = .002) improvements compared with placebo in the key secondary endpoint, change from baseline in CGI-S score at week 4, with statistical differences from placebo observed by week 2 (*P* = .024). Similar findings were reported for other endpoints, including a significantly higher proportion of PANSS responders and CGI-I responders, and significant improvements in PANSS positive, negative, and general psychopathology subscale scores in the OLZ/SAM group compared with placebo. Improvements in these outcomes were similar between the OLZ/SAM and olanzapine groups at all time points. These findings are also consistent with those from prior studies[33–35] examining the acute response to olanzapine in schizophrenia.

Overall, OLZ/SAM was generally well tolerated. The types and rates of AEs with OLZ/SAM were similar to those observed with olanzapine in this study and in previous studies.[34,36,37] Only 2 patients discontinued treatment with OLZ/SAM due to AEs of alanine aminotransferase increase (n = 1) and schizophrenia (worsening of symptoms; n = 1). Interestingly, the rates of parkinsonism, as assessed by SAS total score > 3, were lower in patients treated with OLZ/SAM and olanzapine compared with placebo. A possible explanation for this is an anticholinergic rebound effect in patients in the placebo group as a consequence of stopping their prior antipsychotic medication.[38,39]

The mean increase in weight at week 4 was higher in the OLZ/SAM and olanzapine groups (3.02 and 2.38 kg, respectively) compared with placebo (0.24 kg). However, it should be noted that this 4-week study was designed to assess the antipsychotic efficacy of OLZ/SAM and not to assess the relative weight gain due to olanzapine and OLZ/SAM. In a previously reported phase 2 study[21] of OLZ/SAM with a specific safety focus on weight gain, meaningful differences in weight gain with OLZ/SAM compared with olanzapine were not observed until after 4 weeks of treatment. At the end of 12 weeks, treatment with OLZ/SAM resulted in a significantly lower weight gain than treatment with olanzapine. Fortunately, another study, the 24-week, randomized, double-blind ENLIGHTEN-2 study, will provide additional important data on OLZ/SAM safety in terms of long-term weight changes and will further inform the field.

One limitation of this study was the high placebo response observed at week 4 (LS mean improvement in PANSS total score: −17.5). While a statistical difference from placebo in the primary endpoint was found for both OLZ/SAM and olanzapine, the relative effect size was small. The observed placebo effect is consistent with reported trends in placebo-controlled schizophrenia trials, including those of olanzapine.[34,40] However, olanzapine has been an approved treatment for schizophrenia since 1996, and there is a large body of scientific literature and clinical evidence supporting its efficacy for the treatment of schizophrenia.[36,41–45] An additional limitation of this study is the short duration of 4 weeks. The long-term efficacy and safety of OLZ/SAM remain unknown until the completion of the ongoing studies that are > 4 weeks in duration.

CONCLUSIONS

Treatment with OLZ/SAM resulted in significantly greater antipsychotic efficacy compared with placebo as assessed by PANSS and CGI-S scale scores. OLZ/SAM demonstrated efficacy similar to olanzapine monotherapy. OLZ/SAM was generally well tolerated, with a safety profile in the acute treatment setting similar to olanzapine monotherapy.

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See supplementary material for this article at PSYCHIATRIST.COM.

Supplementary Material

Article Title: Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia: Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study

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List of Supplementary Material for the article

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Summary of prior antipsychotic medications (≥5% of patients overall; Safety Population)

	OLZ/SAM n = 134	Olanzapine n = 133	Placebo n = 134	All N = 401
Patients who took at least 1 prior antipsychotic medication, n (%)	**121 (90.3)**	**119 (89.5)**	**117 (87.3)**	**357 (89.0)**
Risperidone	45 (33.6)	45 (33.8)	34 (25.4)	124 (30.9)
Haloperidol	37 (27.6)	40 (30.1)	45 (33.6)	122 (30.4)
Quetiapine	18 (13.4)	18 (13.5)	24 (17.9)	60 (15.0)
Aripiprazole	13 (9.7)	13 (9.8)	11 (8.2)	37 (9.2)
Amisulpride	6 (4.5)	2 (1.5)	14 (10.4)	22 (5.5)

Abbreviation: OLZ/SAM, olanzapine/samidorphan.

Supplementary Table 2. Summary of extrapyramidal symptom scores from baseline to last on-treatment assessment

Measure	OLZ/SAM n = 134	Olanzapine n = 133	Placebo n = 134
AIMS total score, mean (SD)			
Baseline	0.2 (0.51)	0.2 (0.80)	0.4 (1.40)
Last on-treatment assessment	0.2 (0.91)	0.1 (0.75)	0.2 (0.78)
Change from baseline	0.1 (0.80)	0.0 (0.99)	−0.2 (1.27)
BARS (sum of objective and subjective scores), mean (SD)			
Baseline	0.3 (0.77)	0.3 (0.98)	0.4 (1.15)
Last on-treatment assessment	0.3 (0.86)	0.3 (0.72)	0.3 (0.97)
Change from baseline	0.0 (0.78)	−0.1 (1.04)	−0.1 (0.89)
BARS (global clinical assessment), mean (SD)			
Baseline	0.2 (0.43)	0.2 (0.57)	0.2 (0.64)
Last on-treatment assessment	0.1 (0.39)	0.2 (0.42)	0.2 (0.52)
Change from baseline	0.0 (0.47)	0.0 (0.61)	−0.1 (0.49)
SAS total score, mean (SD)			
Baseline	0.5 (1.02)	0.8 (2.43)	0.8 (2.21)
Last on-treatment assessment	0.4 (0.83)	0.6 (1.46)	0.7 (1.89)
Change from baseline	0.0 (0.78)	−0.3 (1.65)	−0.2 (1.45)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; OLZ/SAM, olanzapine/samidorphan; SAS, Simpson-Angus Scale.

Supplementary Figure 1. Change from Baseline in PANSS Subscales by Week (MMRM; Efficacy population)
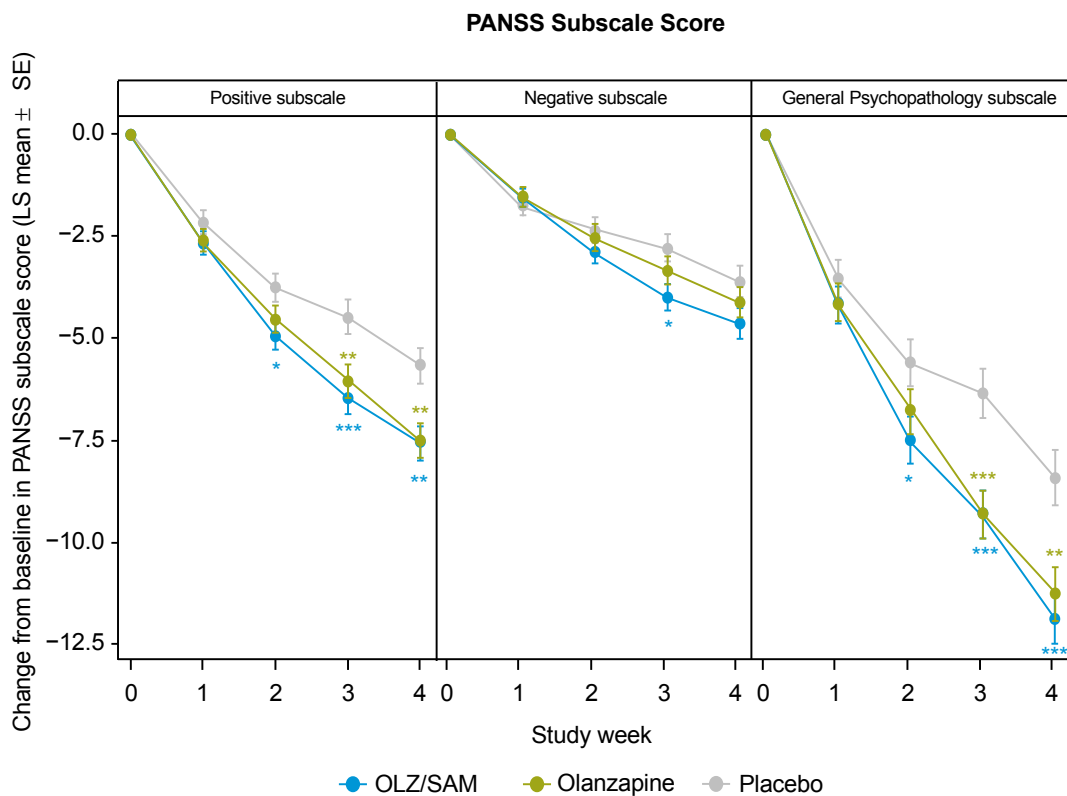
P values vs placebo: *P<0.05; **P<0.01; ***P<0.001.

Abbreviations: LS, least squares; MMRM, mixed model with repeated measurements; OLZ/SAM,

olanzapine/samidorphan; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Supplementary Figure 2. PANSS (≥30% improvement from baseline) (A) and CGI-I (score of ≤2) (B) Responders by Week (LOCF; efficacy population)

A)
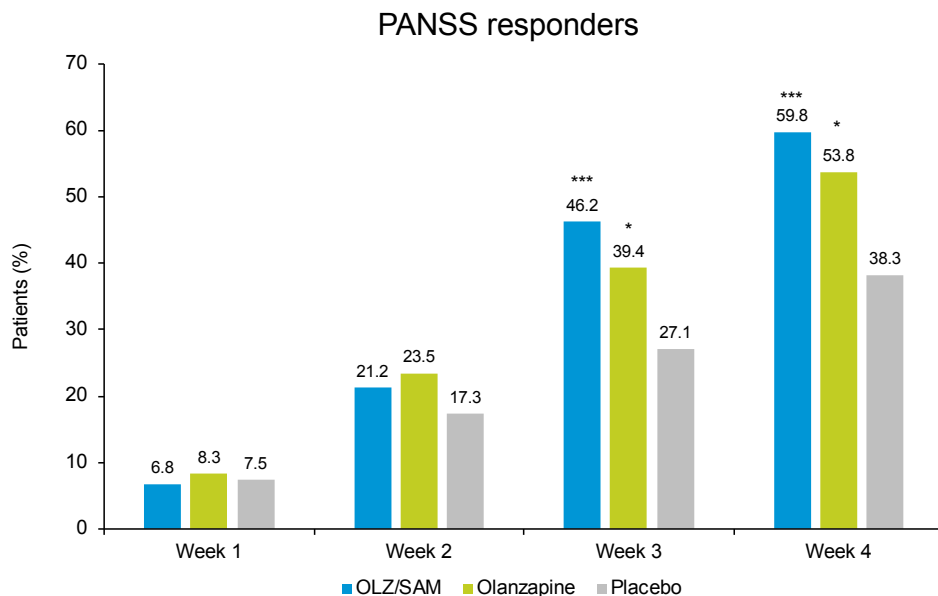
B)

P value vs placebo: **P*<0.05; ***P*≤0.01; ****P*<0.001.

Abbreviations: CGI-I, Clinical Global Impression–Improvement; LOCF, last observation carried forward; OLZ/SAM, olanzapine/samidorphan; PANSS, Positive and Negative Syndrome Scale.

Supplementary Figure 3. Change from Baseline in PANSS Total Score at Week 4 in the Overall Efficacy Population and Key Subgroups for A) OLZ/SAM and olanzapine vs placebo and B) OLZ/SAM vs olanzapine (MMRM approach)

A)

Demographic subgroup categorical value	Forest plot	LS mean difference (95% CI)
Age (years)		
<55 OLZ/SAM vs Placebo (n = 222)		−9.2 (−13.1, −5.3)
Olanzapine vs Placebo (n = 229)		−7.7 (−11.5, −3.8)
≥55 OLZ/SAM vs Placebo (n = 43)		9.8 (0.7, 18.9)
Olanzapine vs Placebo (n = 36)		10.6 (1.0, 20.2)
Gender		
Male OLZ/SAM vs Placebo (n = 161)		−6.7 (−11.3, −2.2)
Olanzapine vs Placebo (n = 158)		−4.9 (−9.5, −0.3)
Female OLZ/SAM vs Placebo (n = 104)		−6.2 (−12.2, −0.3)
Olanzapine vs Placebo (n = 107)		−6.0 (−11.8, −0.1)
Race		
White OLZ/SAM vs Placebo (n = 176)		−9.5 (−13.6, −5.4)
Olanzapine vs Placebo (n = 188)		−8.0 (−12.0, −4.0)
Black OLZ/SAM vs Placebo (n = 79)		3.0 (−4.1, 10.1)
Olanzapine vs Placebo (n = 71)		4.8 (−2.9, 12.4)
Other OLZ/SAM vs Placebo (n = 10)		−12.4 (−36.7, 11.8)
Olanzapine vs Placebo (n = 6)		−5.6 (−42.4, 31.1)
Baseline PANSS Total Score		
<95 OLZ/SAM vs Placebo (n = 72)		−2.8 (−9.2, 3.5)
Olanzapine vs Placebo (n = 81)		−1.7 (−7.8, 4.4)
≥95 OLZ/SAM vs Placebo (n = 193)		−7.9 (−12.3, −3.5)
Olanzapine vs Placebo (n = 184)		−7.2 (−11.7, −2.6)
Overall		
OLZ/SAM vs Placebo (n = 265)		−6.4 (−10.0, −2.8)
Olanzapine vs Placebo (n = 265)		−5.3 (−8.9, −1.7)

−45 −40 −35 −30 −25 −20 −15 −10 −5 0 5 10 15 20 25 30 35 40 45 50

← Favors Active   Favors Placebo →

■ OLZ/SAM vs Placebo   ■ Olanzapine vs Placebo

B)

Demographic subgroup categorical value	Forest plot	LS mean difference (95% CI)
Age (years)		
<55 OLZ/SAM vs olanzapine (n = 219)		−1.5 (−5.4, 2.4)
≥55 OLZ/SAM vs olanzapine (n = 45)		−0.7 (−9.4, 7.9)
Gender		
Male OLZ/SAM vs olanzapine (n = 163)		−1.8 (−6.4, 2.7)
Female OLZ/SAM vs olanzapine (n = 101)		−0.3 (−6.1, 5.6)
Race		
White OLZ/SAM vs olanzapine (n = 184)		−1.5 (5.5, 2.5)
Black OLZ/SAM vs olanzapine (n = 74)		−1.8 (−9.1, 5.5)
Baseline PANSS total score		
<95 OLZ/SAM vs olanzapine (n = 87)		−1.1 (−6.9, 4.6)
≥95 OLZ/SAM vs olanzapine (n = 177)		−0.7 (−5.3, 3.8)
Overall		
OLZ/SAM vs olanzapine (n = 264)		−1.2 (−4.7, 2.4)

−20 −15 −10 −5 0 5 10 15 20

← Favors OLZ/SAM   Favors olanzapine →

■ OLZ/SAM vs olanzapine

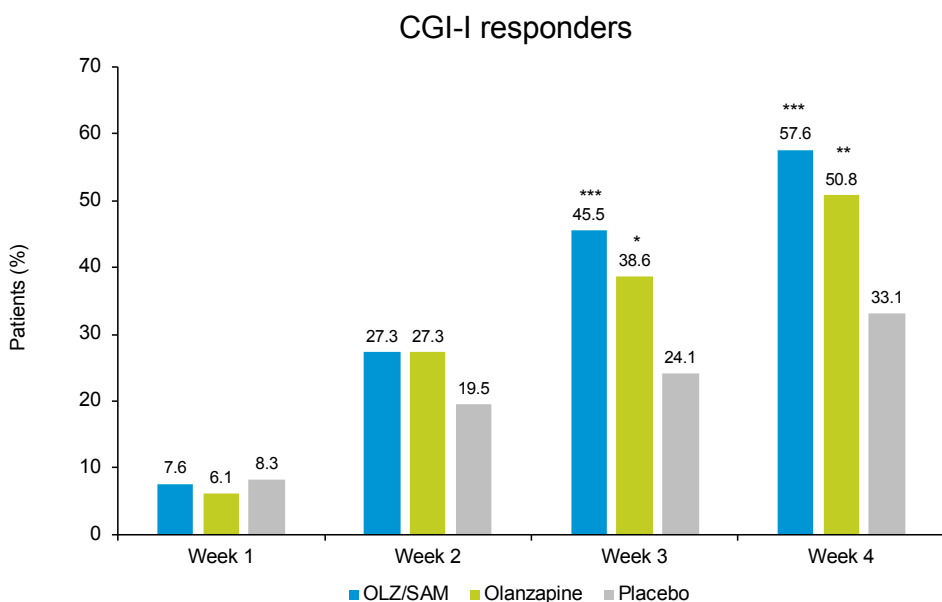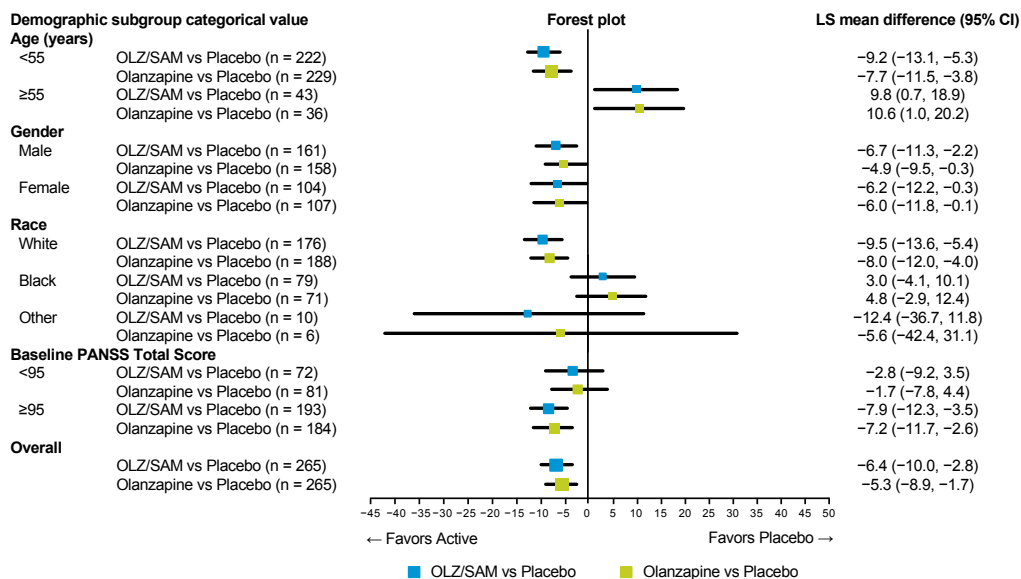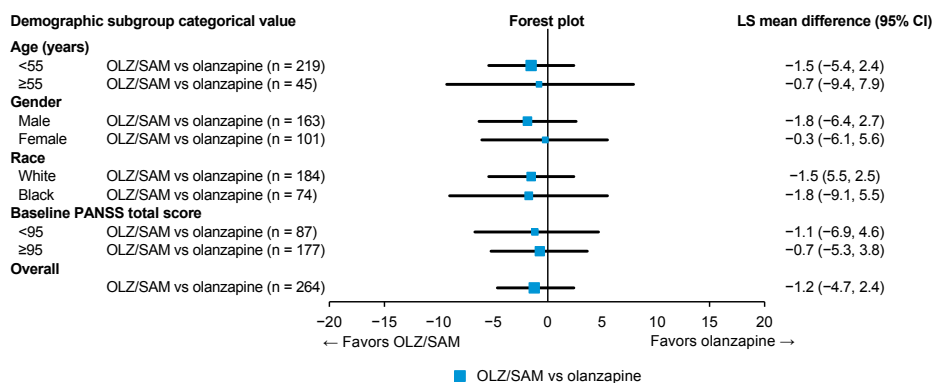Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed-effects model for repeated measures;

OLZ/SAM, olanzapine/samidorphan; PANSS, Positive and Negative Syndrome Scale.