

Effects of Olanzapine Combined With Samidorphan on Weight Gain in Schizophrenia: A 24-Week Phase 3 Study

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Objective: A combination of olanzapine and the opioid receptor antagonist samidorphan is under development for the treatment of schizophrenia and bipolar I disorder. The single-tablet combination treatment is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. In this phase 3 double-blind trial, the authors evaluated the weight profile of combined olanzapine/samidorphan compared with olanzapine in patients with schizophrenia.

Methods: Adults (ages 18–55 years) with schizophrenia were randomly assigned to receive either combination treatment with olanzapine and samidorphan or olanzapine treatment for 24 weeks. Primary endpoints were percent change from baseline in body weight and proportion of patients with $\geq 10\%$ weight gain at week 24. The key secondary endpoint was the proportion of patients with $\geq 7\%$ weight gain. Waist circumference and fasting metabolic laboratory parameters were also measured.

Results: Of 561 patients who underwent randomization (olanzapine/samidorphan combination, N=280; olanzapine, N=281), 538 had at least one postbaseline weight assessment. At week 24, the least squares mean percent weight change from baseline was 4.21% (SE=0.68) in the olanzapine/samidorphan group and 6.59% (SE=0.67) in the olanzapine

group (the difference of -2.38% [SE=0.76] was significant). Significantly fewer patients in the olanzapine/samidorphan combination group compared with the olanzapine group had weight gain $\geq 10\%$ (17.8% and 29.8%, respectively; number needed to treat [NNT]=7.29; odds ratio=0.50) and weight gain $\geq 7\%$ (27.5% and 42.7%, respectively; NNT=6.29; odds ratio=0.50). Increases in waist circumference were smaller in the olanzapine/samidorphan combination group compared with the olanzapine group. Schizophrenia symptom improvement was similar between treatment groups. Adverse events (in $\geq 10\%$ of the groups) in the olanzapine/samidorphan and olanzapine groups included weight gain (24.8% and 36.2%), somnolence (21.2% and 18.1%), dry mouth (12.8% and 8.0%), and increased appetite (10.9% and 12.3%). Metabolic changes were small and similar between treatments.

Conclusions: Olanzapine/samidorphan combination treatment was associated with significantly less weight gain and smaller increases in waist circumference than olanzapine and was well tolerated. The antipsychotic efficacy of the combination treatment was similar to that of olanzapine monotherapy.

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Mental disorders are a leading cause of ill health and disability worldwide (1). Schizophrenia affects 2.4 million people in the United States (2) and is associated with a 3.7-fold increased mortality risk (3). Antipsychotics, including olanzapine, are the cornerstone of treatment of schizophrenia. In long-term effectiveness studies, olanzapine treatment was associated with lower rates of hospitalization for disease exacerbation (4, 5), higher rates of remission (6), and consistently longer time to all-cause discontinuation (4, 5, 7). Despite olanzapine's robust efficacy, the associated risk of significant weight gain and metabolic sequelae (4, 8) has limited its overall clinical utility (9).

Antipsychotic-associated weight gain reduces adherence and leads to treatment switches (10, 11), placing patients at significant risk of relapse, hospitalization, and disease

progression (12). In patient populations already predisposed to shortened lifespan and cardiometabolic risks, weight gain exacerbates this risk. Weight gain also profoundly affects quality of life, psychosocial adaptation, body image, and self-esteem (13, 14), an impact superimposed on the challenges accompanying a psychiatric diagnosis, including stigma and social isolation (15).

Evidence suggests that opioid receptor antagonists may mitigate medication-associated weight gain and/or metabolic dysregulation (16–19). Samidorphan, a new molecular entity, binds in vitro with high affinity to human μ -, κ -, and δ -opioid receptors and acts as an antagonist at μ -opioid receptors and a partial agonist at κ - and δ -opioid receptors (20, 21). In vivo, samidorphan functions as an opioid receptor antagonist (22).

A combination of olanzapine and samidorphan administered as a single tablet is under development for treatment of schizophrenia and bipolar I disorder, and it is hypothesized that the combination treatment would be associated with significantly less weight gain than olanzapine monotherapy. Antipsychotic efficacy of the combination treatment has been established in a phase 3 study in patients with an acute exacerbation of schizophrenia (23). In preclinical studies, co-administration of olanzapine and samidorphan was found to attenuate olanzapine-associated weight gain and mitigate several olanzapine-associated metabolic abnormalities, independently of effects on weight (24). In a 12-week phase 2 dose-ranging study in patients with schizophrenia, combined olanzapine/samidorphan treatment resulted in a 37% reduction in weight gain compared with olanzapine (25). Thus, combined olanzapine/samidorphan treatment may have an improved benefit-risk profile compared with olanzapine, providing an important long-term treatment option with antipsychotic efficacy and the benefit of significantly reduced weight gain (23, 26). This 24-week phase 3 study was specifically designed to evaluate the weight profile of combined olanzapine/samidorphan compared with olanzapine at clinically relevant dosages in adults with schizophrenia.

METHODS

Ethics

The study (ClinicalTrials.gov identifier: NCT02694328) was conducted in accordance with the Declaration of Helsinki, 1964, and Good Clinical Practice principles (International Conference on Harmonization, 1997). The study protocol and all amendments were approved by an institutional review board at each study site.

Patients

Patients 18–55 years of age meeting DSM-5 criteria for a primary diagnosis of schizophrenia were enrolled. Patients were required to be outpatients, have a baseline body mass index (BMI) between 18 and 30, and have stable body weight (self-reported change $\leq 5\%$) for at least 3 months before study initiation.

Key exclusion criteria included a history of treatment-resistant schizophrenia, <1 year elapsed since initial onset of symptoms, naive to antipsychotic medication, active alcohol or substance use disorders (excluding marijuana/tetrahydrocannabinol), or any clinically significant or unstable medical illness (e.g., diabetes, hypo- or hypertension, thyroid dysfunction, and history of seizure disorder or brain tumor) that might compromise patient safety or study endpoint assessments or interfere with the ability to fulfill study requirements. Opioid agonist use within 14 days of screening, opioid antagonist use within 60 days of screening, or anticipated need for opioid treatment during the study were exclusionary, as was the use of olanzapine in the 60 days before screening. All patients provided written informed consent after receiving a complete description of the study.

Study Design

This was a phase 3 multicenter, randomized, double-blind study conducted in the United States. Candidates were screened within 30 days of randomization; eligible patients were randomly assigned in a 1:1 ratio to receive treatment with either combined olanzapine/samidorphan or olanzapine for 24 weeks (see Figure S1A in the online supplement). Study completers were eligible to enroll in a long-term open-label safety study evaluating treatment with combined olanzapine/samidorphan over 52 weeks (ClinicalTrials.gov identifier: NCT02873208); those who elected not to enroll (or who prematurely discontinued the double-blind study) entered a 4-week safety follow-up period.

Study Treatment

The daily doses of combined olanzapine/samidorphan used in this study (10 mg olanzapine/10 mg samidorphan [10/10] and 20 mg olanzapine/10 mg samidorphan [20/10]) represent the lowest and highest approved maintenance dosages of olanzapine for schizophrenia treatment and the intended therapeutic fixed dosage of samidorphan, representing the optimal weight and safety profile when combined with olanzapine (25, 27).

In general, the use of psychotropic medications other than study drug was prohibited, except for beta-blockers, antihistamines, benzodiazepines, and anticholinergics for akathisia or extrapyramidal symptoms. Patients who were taking other antipsychotic medications at study entry were cross-tapered off these medications and titrated onto either combined olanzapine/samidorphan treatment or olanzapine monotherapy over the course of 2 weeks. In the first week, patients received daily doses of combined olanzapine/samidorphan 10/10 or 10 mg olanzapine. The olanzapine dosage was increased to 20 mg/day beginning at week 2. At the end of week 2, 3, or 4, the olanzapine dosage could be lowered to 10 mg/day for tolerability reasons. No dosage adjustments were permitted beyond week 4.

Assessments

Patient visits occurred weekly through week 6, then biweekly for the remaining 18 weeks. Assessments included body weight and waist circumference (both measured in triplicate), vital signs, ECG, adverse events, extrapyramidal symptoms (Abnormal Involuntary Movement Scale [AIMS] [28], Simpson-Angus Scale [29], Barnes Akathisia Rating Scale [30]), the Columbia-Suicide Severity Rating Scale (31), the Positive and Negative Syndrome Scale (PANSS) (32), and the Clinical Global Impressions severity scale (CGI-S) (33). Blood samples for fasting (≥ 8 hours by self-report) metabolic laboratory parameters (triglycerides, cholesterol, glucose, and insulin) and nonfasting hemoglobin A1c were collected.

Primary and Secondary Endpoints

The co-primary endpoints were percent change from baseline at week 24 in body weight and the proportion of patients with $\geq 10\%$ weight gain from baseline at week 24.

The key secondary endpoint was proportion of patients with $\geq 7\%$ weight gain at week 24. The cutoffs of 10% and 7% were selected on the basis of commonly accepted thresholds of clinically significant changes in weight for weight management and psychiatric treatments, respectively.

Statistical Analysis

The initial target sample size was 200 patients per treatment group. This sample size was estimated to provide $\geq 90\%$ power to detect significant differences in mean percent change in body weight of 4% (SD=9%) and in the proportion of patients with $\geq 10\%$ weight gain of 13% at week 24, assuming a cumulative dropout rate of 40%. A prespecified unblinded interim analysis for sample size reestimation was conducted by an independent statistical center when 50% of patients completed the double-blind treatment period or discontinued. Because the conditional power of the co-primary endpoints was less than 90% based on the interim results, the sample size was subsequently increased to 540 patients.

Safety was assessed in patients who received at least one dose of study drug. Weight and antipsychotic efficacy were assessed in all patients who had at least one postbaseline weight assessment.

To control for multiplicity, both co-primary endpoints were tested at an alpha of 0.05 based on the method described by Cui et al. to adjust for the unblinded interim analysis (34). The key secondary endpoint would be tested only if both co-primary endpoints were met.

Missing weight assessments were imputed by multiple imputation sequentially for each visit, using a regression method. The imputation regression model included treatment, race, and baseline age group as factors and body weight at all previous visits (including baseline) as covariates. Five hundred imputations were carried out. The co-primary endpoint of percent change from baseline in body weight at week 24 was analyzed by analysis of covariance (ANCOVA) based on the imputed data sets. The ANCOVA model included treatment, race, and age group as factors and baseline weight as a covariate. Results were combined using Rubin's method. Additional details are provided in the online supplement.

Analysis of the other co-primary endpoint and the key secondary endpoint (proportion of patients with $\geq 10\%$ and $\geq 7\%$ weight gain at week 24, respectively) was carried out using a logistic regression model based on the same multiply imputed weight data as the percent change from baseline in body weight at week 24.

Analyses of change from baseline in body weight and waist circumference at each visit were similar to those of the co-primary endpoint of percent change in body weight at week 24. Change from baseline in metabolic laboratory parameters, PANSS score, and CGI-S score were analyzed using a mixed model with repeated measures; the model included treatment, visit, treatment-by-visit interaction, race, and age group as categorical fixed effects and baseline weight as a

covariate, with an unstructured covariance structure and Kenward-Roger approximation to adjust the denominator degree of freedom.

RESULTS

Patient Disposition and Baseline Characteristics

Of 561 patients who underwent randomization, 550 (combined olanzapine/samidorphan group, N=274; olanzapine group, N=276) entered double-blind treatment (see Figure S1B in the online supplement). In all, 352 (64%) patients completed treatment, with similar completion rates in the two treatment groups. The most common reasons for discontinuation with combined olanzapine/samidorphan and with olanzapine were adverse events (12.0% and 9.8%, respectively), withdrawal by participant (8.4% and 9.8%), and lost to follow-up (8.0% and 9.4%) (see Figure S1B). Randomization was balanced between groups at baseline for demographic characteristics, including race and BMI (Table 1). Only minimal differences were noted between groups on prior antipsychotic medications used before randomization (see Table S1 in the online supplement).

Drug Exposure

Mean olanzapine dosage, calculated as time-weighted average dosage of olanzapine during the entire study, was similar between groups (combined olanzapine/samidorphan group: 16.8 mg/day, SD=3.94; olanzapine group, 16.9 mg/day, SD=3.57), with most patients (79.6%) taking 20 mg/day as the final dosage.

Concomitant Medications

Overall, patients in the combined olanzapine/samidorphan group and in the olanzapine group had similar concomitant medication use during the treatment period (74.1% [203/274] and 76.4% [211/276], respectively). The most frequently used concomitant medications ($\geq 10\%$ of patients in either treatment group) in the combined olanzapine/samidorphan and olanzapine groups were risperidone (20.1% [55/274] and 20.3% [56/276], respectively), ibuprofen (12.4% [34/274] and 10.9% [30/276]), quetiapine fumarate (10.6% [29/274] and 12.0% [33/276]), and aripiprazole (5.8% [16/274] and 10.5% [29/276]). The concomitant use of non-olanzapine antipsychotics reflects patients tapering off their prior antipsychotic medications during the first 2 weeks.

Weight and Metabolic Effects

Weight effects. For the co-primary endpoint, percent change from baseline in body weight at week 24, the least squares mean percent change was 4.21% (SE=0.681%) for the combined olanzapine/samidorphan group and 6.59% (SE=0.668%) for the olanzapine group. The least squares mean difference between the combined olanzapine/samidorphan group and the olanzapine group was -2.38% (SE=0.765%; $p=0.003$) (Figure 1A; see also Table S2 in the online supplement). At each visit from week 6 through week 22, the 95% confidence

TABLE 1. Baseline characteristics of participants in a study of weight gain with combined olanzapine/samidorphan in schizophrenia^a

Characteristic	Combined Olanzapine/ Samidorphan (N=274)		Olanzapine (N=276)	
	Mean	SD	Mean	SD
Age (years)	40.3	9.79	40.1	10.01
	N	%	N	%
Sex				
Male	193	70.4	207	75.0
Female	81	29.6	69	25.0
Race				
Black or African American	199	72.6	193	69.9
White	63	23.0	65	23.6
Asian	4	1.5	4	1.4
American Indian or Alaska Native	2	0.7	2	0.7
Native Hawaiian or other Pacific Islander	1	0.4	0	0
Other	2	0.7	4	1.4
Multiple ^b	3	1.1	8	2.9
	Mean	SD	Mean	SD
Body weight (kg)	77.17	13.69	77.57	13.47
Body mass index	25.38	3.13	25.52	3.19

^a Baseline was defined as the last nonmissing observation before the first dose of study drug.

^b Patients who reported more than one race were counted once under the multiple races category.

intervals for the between-group difference in percent change in weight did not include zero, consistent with the primary endpoint at week 24 (Figure 1A). Weight gain in the combined olanzapine/samidorphan group stabilized from week 6 onward, whereas weight continued to increase in the olanzapine group over the 24-week treatment period. At week 24, the least squares mean change in body weight was 3.18 kg in the olanzapine/samidorphan group and 5.08 kg in the olanzapine group.

Fewer patients receiving combined olanzapine/samidorphan experienced weight gain across a wide range of thresholds for percent change in body weight compared with olanzapine (Figure 1B,C). The proportion of patients with $\geq 10\%$ weight gain at week 24 (co-primary endpoint) was significantly lower in the combined olanzapine/samidorphan group (N=47 [17.8%]) than in the olanzapine group (N=81 [29.8%]; number needed to treat [NNT]=7.29); the odds ratio for $\geq 10\%$ weight gain at week 24 in the combined olanzapine/samidorphan group compared with the olanzapine group was 0.50 (95% CI=0.31, 0.80; $p=0.003$) (see Table S2 in the online supplement).

For the key secondary endpoint, 27.5% of patients in the combined olanzapine/samidorphan group and 42.7% in the olanzapine group experienced $\geq 7\%$ weight gain (NNT=6.29) (Figure 1B,C; see also Table S2 in the online supplement). The odds ratio for $\geq 7\%$ weight gain at week 24 with combined olanzapine/samidorphan compared with olanzapine was 0.50 (95% CI=0.33, 0.76; $p=0.001$) (see Table S2).

Waist circumference. At week 24, the least squares mean change from baseline in waist circumference was 2.36 cm

(SE=0.561) in the combined olanzapine/samidorphan group and 4.47 cm (SE=0.546) in the olanzapine group (least squares mean difference: -2.12 cm [SE=0.628]; 95% CI= -3.35 , -0.89). Separation in waist circumference occurred early, with smaller increases in waist circumference in the combined olanzapine/samidorphan group compared with the olanzapine group at all visits. Initially at week 1, and then at each visit from week 4 through week 24, the 95% confidence intervals for the between-group difference in waist circumference did not include zero (Figure 2). At week 24, 26.8% of the combined olanzapine/samidorphan group and 43.2% of the olanzapine group had a waist circumference increase

of ≥ 5 cm, a finding associated with increased mortality risk (35); the risk difference was -17.1% (95% CI= -26.3 , -7.8 ; odds ratio=0.47; NNT=5.86).

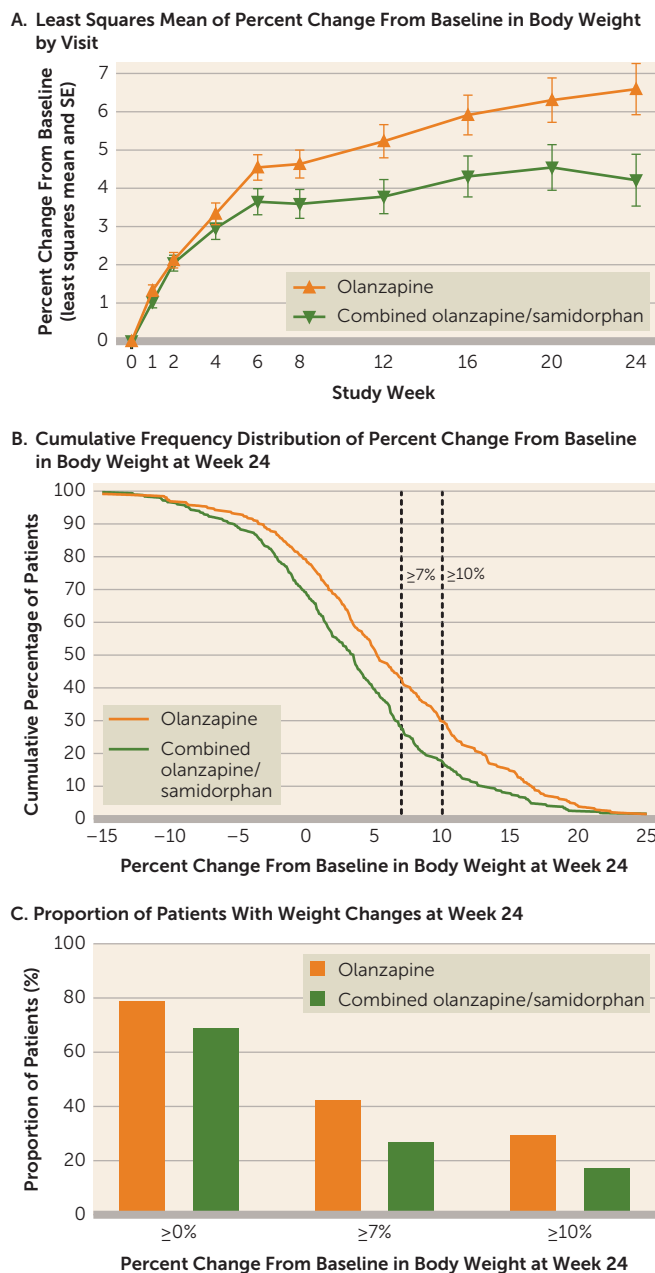
Metabolic laboratory parameters. Changes from baseline to week 24 in glycemic and lipid laboratory parameters were generally small and similar for the two treatment groups and tended to occur early (Table 2). The largest changes in any of these parameters were in triglyceride levels, where least squares mean increases of 26.77 mg/dL (SE=5.78) and 29.36 mg/dL (SE=5.69) were observed in the combined olanzapine/samidorphan and olanzapine groups, respectively.

Safety

Adverse events were reported in 74.1% and 82.2% of the combined olanzapine/samidorphan and olanzapine groups, respectively. The most commonly reported adverse events ($\geq 10\%$) in the two groups were weight increase (24.8% and 36.2%, respectively), somnolence (21.2% and 18.1%), dry mouth (12.8% and 8.0%), and increased appetite (10.9% and 12.3%) (Table 3). Most adverse events were mild to moderate in severity. Twelve percent of patients in the combined olanzapine/samidorphan group discontinued treatment because of an adverse event, compared with 9.8% in the olanzapine group (Table 3; see also Figure S1B in the online supplement).

No deaths occurred during the study, and serious adverse events were reported in 3.6% and 2.5% of patients in the combined olanzapine/samidorphan and olanzapine groups, respectively (Table 3). The only serious adverse event occurring in more than one patient was worsening/

FIGURE 1. Change from baseline in body weight in a study of weight gain with combined olanzapine/samidorphan in schizophrenia^a

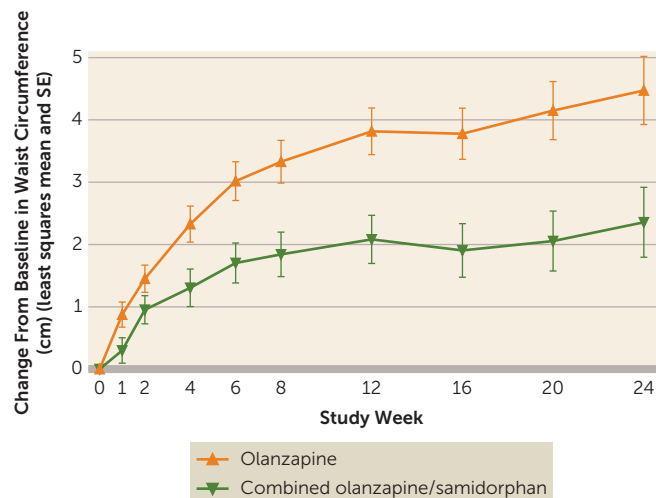


^a Missing postbaseline assessments were imputed based on multiple imputation. Data in panel A were analyzed using an analysis of covariance model with treatment, race (black/African American, nonblack/non-African American), and age group (<30 years, ≥30 years) as factors and baseline body weight as the covariate. Baseline was defined as the last nonmissing value before the first dose of study drug.

exacerbation of schizophrenia symptoms (one patient [0.4%] in the combined olanzapine/samidorphan group and three patients [1.1%] in the olanzapine group).

There were no clinically meaningful changes or differences observed in vital signs, ECG results, movement disorder scale scores (AIMS, Simpson-Angus Scale, or Barnes

FIGURE 2. Least squares mean change from baseline in waist circumference by visit in a study of weight gain with combined olanzapine/samidorphan in schizophrenia^a



^a Waist circumference analysis was based on an analysis of covariance (ANCOVA) model with a multiple imputation approach for missing postbaseline assessments. The ANCOVA model included treatment, race (black/African American, nonblack/non-African American), and age group (<30 years, ≥30 years) as factors and baseline body weight as the covariate. Baseline was defined as the last nonmissing value before the first dose of study drug.

Akathisia Rating Scale), or Columbia-Suicide Severity Rating Scale scores for patients in the two treatment groups.

The overall safety profile of combined olanzapine/samidorphan in this 24-week study was consistent with that of olanzapine, except for fewer adverse events of weight increase in the combined olanzapine/samidorphan group.

Antipsychotic Efficacy

PANSS and CGI-S scores. The mean PANSS total score at baseline was 68.2 (SD=9.51) in the combined olanzapine/samidorphan group and 70.2 (SD=9.47) in the olanzapine group. The PANSS total score improved similarly in both groups; the least squares mean change from baseline to week 24 was −8.2 (SE=0.73) in the combined olanzapine/samidorphan group and −9.4 (SE=0.72) in the olanzapine group. The least squares mean difference between treatments was 1.2 (95% CI=−0.9, 3.2). Reductions in CGI-S score from baseline to week 24 were similar between the two treatment groups, consistent with the changes in PANSS total score (see Figure S4 in the online supplement).

DISCUSSION

In this 24-week study in patients with schizophrenia, treatment with combined olanzapine/samidorphan resulted in significantly less weight gain compared with olanzapine monotherapy. Differences in weight gain were apparent at week 6 and remained lower in the combined olanzapine/samidorphan group at each subsequent visit through week 24. The weight distribution profile in the combined

TABLE 2. Analysis of change from baseline in fasting glycemic and lipid parameters in a study of weight gain with combined olanzapine/samidorphan in schizophrenia^a

Parameter	Baseline		Change From Baseline to Week 2		Change From Baseline to Week 4		Change From Baseline to Week 8		Change From Baseline to Week 12		Change From Baseline to Week 24	
	OLZ/SAM	Olanzapine	OLZ/SAM	Olanzapine	OLZ/SAM	Olanzapine	OLZ/SAM	Olanzapine	OLZ/SAM	Olanzapine	OLZ/SAM	Olanzapine
Total cholesterol (mg/dL)												
N	265	270	230	256	223	234	206	222	198	207	162	166
Mean	183.4	185.2	9.3	6.8	7.3	7.5	5.8	5.1	3.4	4.5	0.9	2.1
SD	34.74	37.27	26.25	24.60	23.87	25.60	27.62	26.85	26.42	24.68	28.18	28.88
HDL cholesterol (mg/dL)												
N	265	270	230	256	223	234	206	222	198	207	162	166
Mean	62.4	62.1	-0.4	0.2	-1.7	-0.8	-3.7	-2.5	-3.6	-3.3	-5.1	-4.5
SD	22.42	21.02	10.39	10.11	12.00	12.22	11.48	11.59	12.97	12.90	15.20	11.35
LDL cholesterol (mg/dL)												
N	264	270	229	256	222	234	206	222	197	207	161	166
Mean	109.6	112.7	8.3	3.6	6.7	5.6	6.1	3.7	4.4	4.1	0.6	0.9
SD	32.26	33.98	22.48	20.80	22.11	22.08	25.80	24.30	24.24	21.62	26.37	26.51
Triglycerides (mg/dL)												
N	265	270	230	256	223	234	206	222	198	207	162	166
Mean	114.4	107.1	12.7	24.0	15.7	17.2	21.3	24.1	16.6	19.8	23.9	24.5
SD	93.96	62.14	71.16	70.17	59.52	64.83	78.17	77.55	75.91	65.43	78.29	71.49
Glucose (mg/dL)												
N	265	270	231	256	225	237	206	220	197	206	160	166
Mean	90.3	91.4	6.2	1.9	3.4	2.3	3.6	1.7	4.2	1.9	4.5	2.3
SD	11.60	12.03	17.43	14.28	13.42	15.54	14.69	15.12	15.49	13.75	15.05	15.70
Insulin (μIU/mL)												
N	265	269	227	249	220	230	205	217	196	203	162	161
Mean	12.65	12.12	4.23	5.49	4.43	2.57	3.41	3.23	2.32	1.96	3.22	3.40
SD	20.87	15.85	19.78	28.61	26.32	19.41	20.16	17.61	26.43	20.72	28.72	15.60
HbA _{1c} ^b (%)												
N	266	272	243	264	235	247	218	234	211	216	173	173
Mean	5.40	5.40	0.03	0.04	0.04	0.02	-0.01	0.03	0.00	0.04	0.06	0.07
SD	0.38	0.42	0.20	0.21	0.26	0.21	0.30	0.26	0.30	0.27	0.27	0.27

^a Analyzed using a mixed model with repeated measures, which includes the treatment, visit, treatment-by-visit interaction, race (black or African American, non-black or non-African American), and age group (<30 years, ≥30 years) as factors and the corresponding baseline value as the covariate. OLZ/SAM=combination olanzapine/samidorphan.

^b Nonfasting.

olanzapine/samidorphan group was shifted compared with the olanzapine group, such that fewer patients gained weight across a range of cutoffs. Not only were patients less likely to gain any weight with combined olanzapine/samidorphan, but also the risk of clinically significant weight gain (of ≥7% and of ≥10%) was reduced by 50% relative to olanzapine.

The results of this study extend those of a previous study in which combined olanzapine/samidorphan treatment was associated with significantly less weight gain compared with olanzapine over 12 weeks (25). In both studies, combined olanzapine/samidorphan treatment resulted in weight gain over the first 4 to 6 weeks before stabilizing. The mean increase in weight in this study was 3.18 kg in the combined olanzapine/samidorphan group and 5.08 kg in the olanzapine group at 24 weeks. Some degree of weight gain is commonly reported in clinical trials with other atypical antipsychotics during periods beyond 6 months. For example, weight increases with brexpiprazole (1.3 kg) (36), cariprazine (1.7 kg) (37), quetiapine (2.4–3.7 kg) (38, 39), and risperidone (4.3 kg) (40) have been reported. Comparisons to other antipsychotics must be interpreted cautiously owing to different study objectives, designs, populations, and analyses. Nonetheless, the data suggest that while combined olanzapine/samidorphan may be associated with more weight gain than

some atypical antipsychotics, it may be within the range of weight gain seen in commonly used treatments, such as risperidone and quetiapine.

In addition to less weight gain, combined olanzapine/samidorphan was also associated with significantly smaller increases in waist circumference compared with olanzapine. Waist circumference is a proxy for central fat accumulation (41), and increases in waist circumference have been associated with a greater risk of cardiovascular disease and diabetes, even independently of weight (41, 42). The separation in waist circumference for combined olanzapine/samidorphan versus olanzapine occurred earlier than the separation in weight, suggesting that while weight gain was similar during the first 6 weeks, it may have been distributed differently. A shift away from increasing abdominal adiposity may potentially lead to a reduction of cardiovascular and diabetes risk with combined olanzapine/samidorphan in comparison to olanzapine, especially long-term. For patients treated with combined olanzapine/samidorphan, the risk of having a waist circumference increase of ≥5 cm was reduced by approximately 50% compared with olanzapine. A 5-cm increase in waist circumference is clinically relevant, as it not only represents a change in pant size for the average adult but also is associated with an increased mortality risk (9% in women and 7% in men) (35).

TABLE 3. Overview of adverse events during the double-blind treatment period in a study of weight gain with combined olanzapine/samidorphan in schizophrenia^a

Category	Combined Olanzapine/ Samidorphan (N=274)		Olanzapine (N=276)	
	N	%	N	%
Any adverse event	203	74.1	227	82.2
Adverse event by severity				
Mild	106	38.7	125	45.3
Moderate	87	31.8	95	34.4
Severe	10	3.6	7	2.5
Adverse event leading to treatment discontinuation	33	12.0	27	9.8
Any serious adverse event	10	3.6	7	2.5
Adverse events in ≥5% of patients in either group				
Weight increased	68	24.8	100	36.2
Somnolence	58	21.2	50	18.1
Dry mouth	35	12.8	22	8.0
Increased appetite	30	10.9	34	12.3
Waist circumference increased	17	6.2	22	8.0
Blood creatine phosphokinase increased	14	5.1	12	4.3
Extra dose administered	14	5.1	17	6.2

^a If a patient experienced more than one adverse event in a category, the patient was counted only once in that category. Percentages were based on the number of patients who received at least one dose of study drug. Adverse events of dizziness, sedation, and constipation, previously reported to differ with samidorphan addition (up to 20 mg) relative to olanzapine monotherapy (25), occurred at the following frequencies in the combined olanzapine/samidorphan and olanzapine groups, respectively: dizziness (N=9 [3.3%] and N=12 [4.3%]); sedation (N=11 [4.0%] and N=12 [4.3%]); and constipation (N=7 [2.6%] and N=5 [1.8%]). Dosages of combined olanzapine/samidorphan were 10 or 20 mg/day olanzapine with 10 mg/day samidorphan. Olanzapine was given in dosages of 10 or 20 mg/day.

A notable finding in this study was that there were no differences between combined olanzapine/samidorphan and olanzapine on the metabolic laboratory parameters assessed, despite differences in weight gain and waist circumference increase. Changes in fasting lipid and glycemic parameters with olanzapine treatment were generally small at 24 weeks, limiting the ability to detect differences with combined olanzapine/samidorphan. The lack of a more pronounced metabolic effect with olanzapine seems to be at odds with the increased risk of diabetes and dyslipidemia associated with olanzapine treatment in clinical practice (43, 44). While the changes in fasting lipid and glycemic parameters observed over 24 weeks in this study were consistent with what has been reported for olanzapine in some studies of similar duration (38, 45–47), generally a higher risk of cardiometabolic adverse effects would be expected with olanzapine (48–50). While weight gain is consistently observed with olanzapine across studies, metabolic effects are more variable. This variability may be related to differences in study designs, patient populations, and analysis methods, making it difficult to generalize across studies. Finally, as this study did not directly compare combined olanzapine/samidorphan with non-olanzapine antipsychotics in similar populations, the overall metabolic risk relative to these medications is unclear. Additional studies designed to evaluate the comparative metabolic risk of combined olanzapine/samidorphan and various other antipsychotics are warranted.

Notably, the timing of changes in metabolic laboratory parameters was an important factor in this study. For both treatments, changes in metabolic laboratory parameters generally occurred early, within the first few weeks, with little additional change over the remainder of the treatment period. The continued weight increases observed with olanzapine did not translate to any clear metabolic worsening beyond these initial effects. As a result, mitigation of weight gain by combined olanzapine/samidorphan did not lead to a discernible metabolic benefit in this study. This finding points to a potential pitfall in trying to relate olanzapine-associated metabolic changes solely to changes in body weight. Several studies have documented the effects of olanzapine on lipid and glucose metabolism within days of initiating treatment (51–53). These early metabolic effects appear to be more directly related to the drug itself rather than to secondary consequences of weight gain. The time frame over which these initial changes persist or give way to the longer-term secondary changes associated with accumulating weight is not well understood. The 6-month duration of this study may have been insufficient to detect these secondary weight-related changes in metabolic risk factors; thus, any potential metabolic effects derived from mitigating weight gain with combined olanzapine/samidorphan may have been missed.

While a metabolic benefit for combined olanzapine/samidorphan relative to olanzapine was not observed in this study, extensive evidence supports the expectation that mitigation of olanzapine-associated weight gain should ultimately lead to metabolic benefit. Olanzapine-associated weight gain poses such a relevant safety risk because it continues over long-term treatment, with a majority of patients gaining substantial amounts of weight over periods well exceeding the 6-month time frame of this study (27, 54, 55). In 293 patients treated with olanzapine for a median of 2.5 to 3 years, 22% gained 10–20 kg, and 9% gained more than 20 kg (54). Epidemiologic evidence suggests that gaining as little as 5 kg can result in an increased risk of cardiovascular disease and diabetes, and this risk escalates further with weight gain of more than 20 kg (56). Similarly, the risk of cardiovascular mortality increases exponentially as patients transition from

being overweight to obese (57). Obesity is also associated with numerous other health complications, including asthma, gallbladder disease, osteoarthritis, and chronic back pain (58). By stabilizing weight after the initial 4 to 6 weeks of treatment and shifting the weight gain distribution so that fewer patients gain substantial amounts of weight, combined olanzapine/samidorphan will likely have a noticeable health benefit relative to olanzapine over time. Moreover, as mentioned above, a metabolic benefit may also be afforded by reduced central fat accumulation compared with olanzapine. Ongoing safety studies (ClinicalTrials.gov identifiers: NCT02873208, NCT02669758, NCT03201757) are assessing the long-term effects of combined olanzapine/samidorphan on weight and metabolic laboratory parameters, and results will further inform the relative cardiometabolic effects of this drug combination.

There are currently no treatments approved by the U.S. Food and Drug Administration to address antipsychotic-associated weight gain (11). Several approaches have been explored, including adjunctive metformin and switching to or supplementing treatment with an antipsychotic with a lower weight-gain liability (e.g., aripiprazole) (59). Metformin is one of the most well-studied approaches (60, 61). Many of the metformin studies investigated reversal of olanzapine or other antipsychotic-associated weight gain rather than prevention (as in the present study), although there are some studies in which prevention was assessed. While metformin has the potential to reverse and even prevent olanzapine-associated weight gain (62–67), these results must be interpreted cautiously, given the variability in effects and effect sizes, small sample sizes (typically fewer than 100 patients total), and short assessment periods (several studies had durations shorter than 24 weeks). Moreover, study designs varied widely (e.g., inpatient versus outpatient, early-episode patients versus patients with established disease, and inclusion of only Chinese populations or of lifestyle modifications, such as calorie restrictions and exercise programs). Of note, the present study explicitly discouraged changes in lifestyle to more accurately focus on weight differences due to treatment. While adjunctive lifestyle approaches may prove useful in limiting olanzapine-associated weight gain (68), combined olanzapine/samidorphan is intended to be taken as a single tablet that provides the antipsychotic effect of olanzapine with significantly less associated weight gain.

In this study, treatment with combined olanzapine/samidorphan and with olanzapine resulted in similar improvements in symptoms of schizophrenia as reflected in PANSS and CGI-S scores. Also, combined olanzapine/samidorphan was generally well tolerated, with a safety profile consistent with that of olanzapine.

The exact mechanism of action of combined olanzapine/samidorphan is unknown. Data from preclinical animal models suggest that olanzapine induces weight and metabolic changes, and that samidorphan attenuates olanzapine-associated changes in fat mass via blockade of adipose glucose uptake and/or by preventing olanzapine-induced insulin

resistance. Importantly, these effects occurred in the absence of increased food consumption or altered eating behaviors. We refer the reader to Cunningham and colleagues' recent publication of these data (24). However, this remains an area of active research, as many aspects of the mechanism of action of combined olanzapine/samidorphan are not understood.

Several limitations of this study may have affected the results. First, almost 40% of patients discontinued the study early, leading to a relatively high volume of missing data. This discontinuation rate is consistent with discontinuation rates reported in other 6-month studies of antipsychotics in patients with schizophrenia (45, 69). Here, the multiple imputation approach to handling missing data was appropriate and was supported by the results of the sensitivity analyses. Additional study limitations included fasting status based solely on self-report, without independent confirmation (i.e., samples may not have been truly fasting in all cases). Moreover, the restrictive BMI criterion for study entry (a BMI in the range of 18–30) in patients with long illness and antipsychotic treatment histories (mean age, approximately 40 years; most frequent prior antipsychotics, risperidone and quetiapine) may have inadvertently selected patients who were relatively resistant to antipsychotic-associated weight gain and metabolic dysregulation. Also, patients older than 55 years were excluded from the study. Ongoing studies will provide additional data on the weight and metabolic effects of combined olanzapine/samidorphan in patients with minimal prior antipsychotic exposure (ClinicalTrials.gov identifier: NCT03187769) and patients continuing treatment over several years (ClinicalTrials.gov identifier: NCT03201757).

Given the complexity and heterogeneity of schizophrenia, there is no single treatment that will work for every patient over the entire course of illness. Patients and clinicians need more treatment options to effectively manage symptoms while limiting side effect burden (70). Combined olanzapine/samidorphan provides a potential new treatment option that possesses the antipsychotic efficacy of olanzapine with significantly less weight gain. Initial weight gain has still been observed with combined olanzapine/samidorphan over the first 4 to 6 weeks, and this must be factored into any benefit-risk assessment. However, by mitigating weight gain after this initial period and reducing the number of patients who have substantial increases in weight and waist circumference, combined olanzapine/samidorphan mitigates one of the key safety risks of olanzapine that has limited its clinical use.

In conclusion, combined olanzapine/samidorphan was found to mitigate the important side effect of olanzapine-associated weight gain while maintaining the established antipsychotic efficacy of olanzapine. While the metabolic changes observed at week 24 were similar between treatments, treatment with combined olanzapine/samidorphan resulted in a clinically meaningful mitigation of weight gain and increases in waist circumference, two well-established risk factors for cardiovascular disease and diabetes. Thus, combined olanzapine/samidorphan represents a potential new treatment option for patients.

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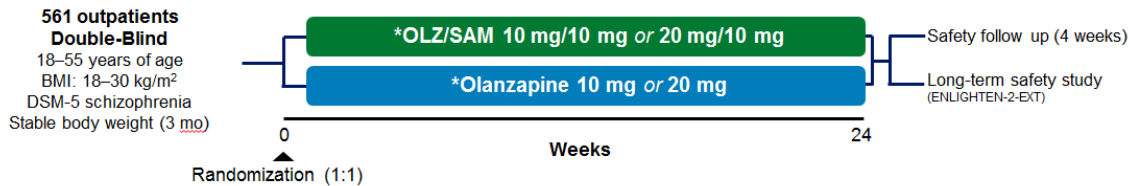
Statistics

Primary Analysis of Co-primary and Key Secondary Endpoints

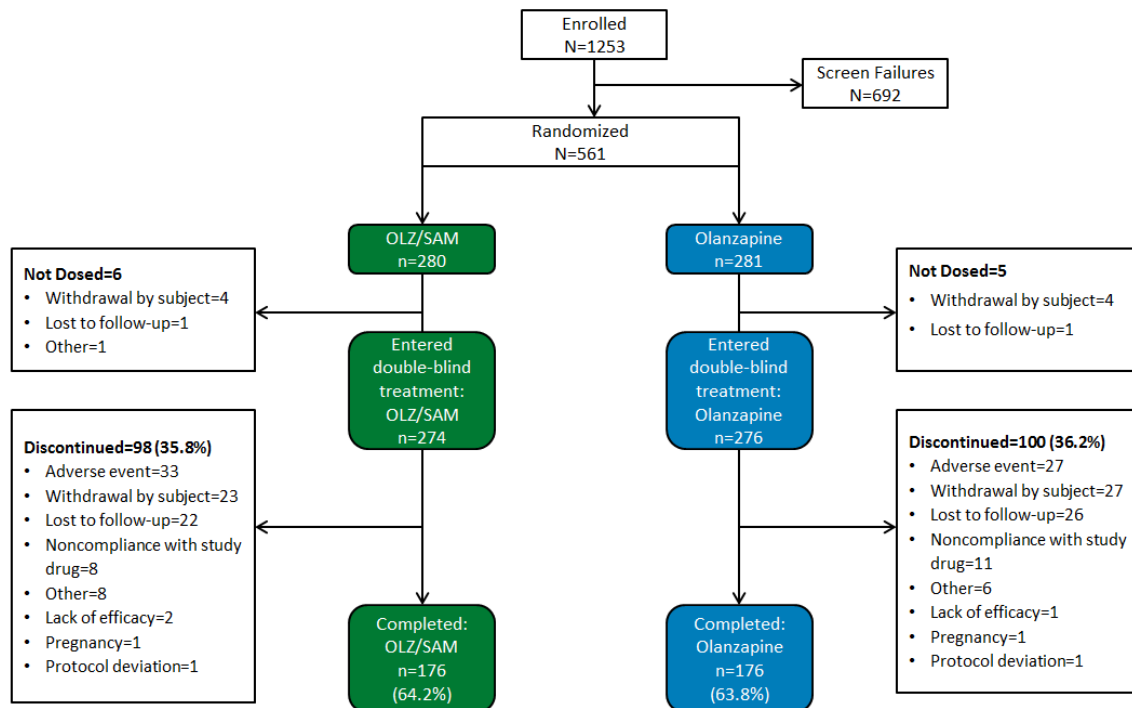
Sensitivity Analysis of Co-primary and Key Secondary Endpoints

Figure S1. A) Study design and B) patient disposition

A



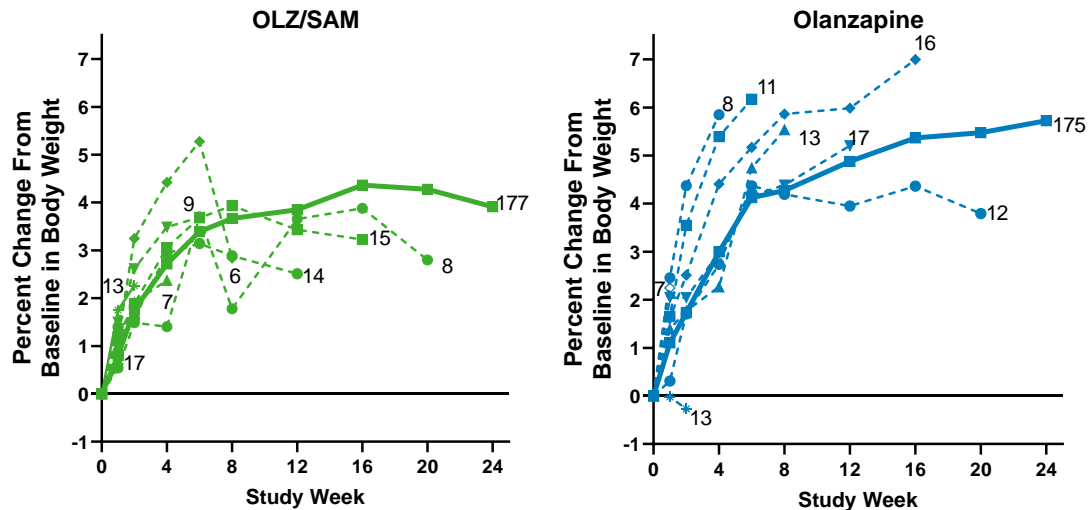
B



*Initial olanzapine dose was 10 mg (both groups), with up-titration to 20 mg at the end of week 1. Down-titration back to 10 mg olanzapine was permitted in either group at the end of weeks 2, 3, or 4 if there were tolerability issues based on the investigator's judgment; the olanzapine dose was fixed from week 4 to 24. At the conclusion of the study, patients had the option of entering a long-term, 52-week safety extension study. If patients declined participation in the extension, or terminated early, they entered the 4-week safety follow-up period.

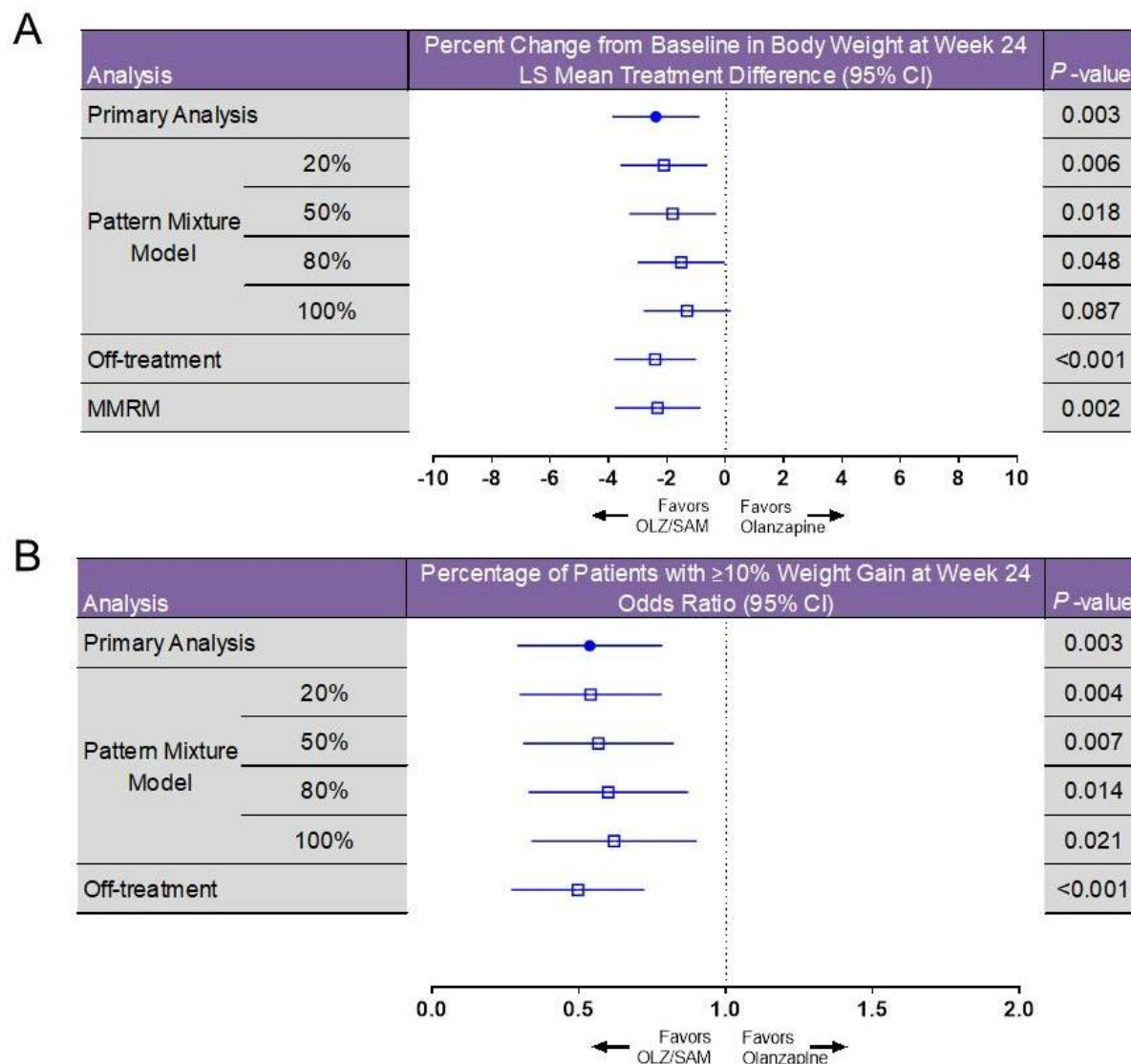
BMI, body mass index; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; OLZ/SAM, combination of olanzapine and samidorphan.

Figure S2. Weight gain trajectory in patients with early discontinuation vs patients who completed the study



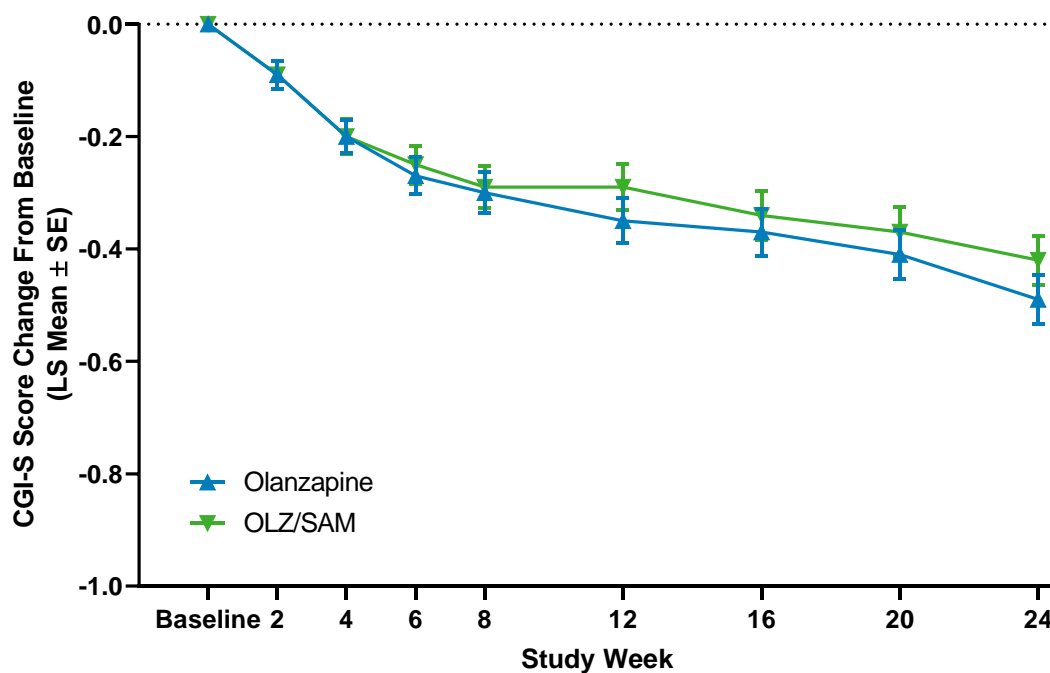
Solid lines denote the weight gain curve of patients who completed the study. Dashed lines denote patients who prematurely discontinued at given visits. Numbers of patients summarized by each curve are noted. In the OLZ/SAM group, weight gain profiles of discontinuing patients were not much different visually from those of completing patients. In the olanzapine group, many of the discontinuing patients had experienced substantial weight gain vs completers. There were a subset of patients randomized to olanzapine who lost weight prior to treatment discontinuation (n=13) in week 2, which was not the case for any patients who received OLZ/SAM and discontinued. LS, least squares; MMRM, mixed-model repeated measures; OLZ/SAM, combination of olanzapine and samidorphan.

Figure S3. Sensitivity analysis on missing data for co-primary endpoints at week 24: (A) percent change from baseline in body weight and (B) percentage of patients with clinically significant weight gain ($\geq 10\%$)



LS, least squares; MMRM, mixed-model repeated measures; OLZ/SAM, combination of olanzapine and samidorphan.

Figure S4. LS mean (SE) change from baseline^a in CGI-S score by visit (MMRM)



CGI-S, Clinical Global Impression-Severity; MMRM, mixed-model repeated measures; OLZ/SAM, combination of olanzapine and samidorphan.

^aMean (SD) CGI-S scores at baseline: olanzapine, 3.66 (0.526); OLZ/SAM, 3.53 (0.550).

Table S1. Summary of medications used by at least 2% patients in either treatment group in the 60 days prior to screening

Medication	OLZ/SAM (N=274) n (%)	Olanzapine (N=276) n (%)
Patients who took ≥1 prior medication	234 (85.4)	236 (85.5)
Risperidone	92 (33.6)	84 (30.4)
Quetiapine fumarate	43 (15.7)	49 (17.8)
Aripiprazole	24 (8.8)	36 (13.0)
Trazodone	29 (10.6)	27 (9.8)
Benztropine mesylate	22 (8.0)	28 (10.1)
Ibuprofen	21 (7.7)	20 (7.2)
Quetiapine	17 (6.2)	15 (5.4)
Haloperidol	15 (5.5)	15 (5.4)
Valproate semisodium	10 (3.6)	14 (5.1)
Diphenhydramine hydrochloride	8 (2.9)	12 (4.3)
Lurasidone hydrochloride	8 (2.9)	12 (4.3)
Mirtazapine	10 (3.6)	10 (3.6)
Salbutamol	10 (3.6)	10 (3.6)
Fluoxetine	10 (3.6)	6 (2.2)
Hydrochlorothiazide	6 (2.2)	10 (3.6)
Lorazepam	8 (2.9)	8 (2.9)
Amlodipine	7 (2.6)	8 (2.9)
Bupropion hydrochloride	9 (3.3)	6 (2.2)
Citalopram	4 (1.5)	11 (4.0)
Sertraline hydrochloride	4 (1.5)	11 (4.0)
Simvastatin	8 (2.9)	7 (2.5)
Clonazepam	7 (2.6)	7 (2.5)
Paliperidone	5 (1.8)	9 (3.3)
Paracetamol	8 (2.9)	6 (2.2)
Hydroxyzine	5 (1.8)	8 (2.9)
Lisinopril	7 (2.6)	6 (2.2)
Omeprazole	9 (3.3)	3 (1.1)
Alprazolam	9 (3.3)	2 (0.7)
Acetylsalicylic acid	4 (1.5)	6 (2.2)
Amlodipine besilate	6 (2.2)	4 (1.4)
Sertraline	6 (2.2)	4 (1.4)
Gabapentin	3 (1.1)	6 (2.2)
Ziprasidone hydrochloride	3 (1.1)	6 (2.2)
Zolpidem	6 (2.2)	2 (0.7)

OLZ/SAM, combination of olanzapine and samidorphan.

Table S2. Body weight changes and odds ratios of clinically significant weight gain from baseline to week 24

	OLZ/SAM (N=266)	Olanzapine (N=272)
Body weight		
Stage 1 subjects (before interim analysis), n	98	102
Baseline, mean \pm SD, kg	77.98 \pm 13.69	76.76 \pm 13.36
Week 24, mean \pm SD, kg ^a	80.95 \pm 15.45	81.26 \pm 15.42
Percent change from baseline body weight at week 24		
Mean \pm SD ^a	3.87 \pm 8.63	5.84 \pm 7.59
LS mean \pm SE ^b	3.08 \pm 1.17	4.91 \pm 1.22
95% CI ^b	(0.79, 5.36)	(2.51, 7.31)
LSMD \pm SE vs olanzapine ^b	-1.83 \pm 1.30	
95% CI ^b	(-4.38, 0.72)	
Test statistic ^c	-1.41	
Stage 2 subjects (after interim analysis), n	168	170
Baseline, mean \pm SD, kg	76.43 \pm 13.69	77.86 \pm 13.57
Week 24, mean \pm SD, kg ^a	78.88 \pm 14.12	82.54 \pm 15.23
Percent change from baseline body weight at week 24		
Mean \pm SD ^a	3.47 \pm 7.31	6.15 \pm 8.49
LS mean \pm SE ^b	4.70 \pm 0.85	7.42 \pm 0.79
95% CI ^b	(3.04, 6.36)	(5.87, 8.96)
LSMD \pm SE vs olanzapine ^b	-2.72 \pm 0.95	
95% CI ^b	(-4.58, -0.85)	
Test statistic ^c	-2.86	
Final analysis, n	266	272
Baseline, mean \pm SD, kg	77.00 \pm 13.68	77.45 \pm 13.48
Week 24, mean \pm SD, kg ^a	79.67 \pm 14.64	82.02 \pm 15.24
Mean change from baseline to week 24 \pm SE, kg ^a	3.18 \pm 0.52	5.08 \pm 0.50
Percent change from baseline body weight at week 24		
Mean \pm SD ^a	3.65 \pm 7.79	6.00 \pm 8.14
LS mean \pm SE ^b	4.21 \pm 0.68	6.59 \pm 0.67
95% CI ^b	(2.88, 5.6)	(5.28, 7.90)
LSMD \pm SE vs olanzapine ^b	-2.38 \pm 0.77	
95% CI ^b	(-3.88, -0.88)	
Adjusted test statistic ^c	-3.01	
Adjusted P value ^c	0.003	
Proportions of patients with $\geq 10\%$ weight gain		
Stage 1 subjects (before interim analysis), n	98	102
$\geq 10\%$ weight gain, n (%) ^d	18 (18.2)	28 (27.9)
<10% weight gain, n (%) ^d	80 (81.8)	74 (72.1)
Risk difference vs olanzapine ^b , %	-9.3	
95% CI ^b	(-22.3, 3.7)	
Odds ratio for $\geq 10\%$ weight gain vs olanzapine ^b	0.57	
95% CI ^b	(0.27, 1.23)	
Test statistic	-1.42	
Stage 2 subjects (after interim analysis), n	168	170
$\geq 10\%$ weight gain, n (%) ^d	29 (17.3)	53 (31.4)
<10% weight gain, n (%) ^d	139 (82.7)	117 (68.6)
Risk difference vs olanzapine ^b , %	-17.2	
95% CI ^b	(-29.1, -5.2)	

Odds ratio for $\geq 10\%$ weight gain vs olanzapine ^b	0.43	
95% CI ^b	(0.24, 0.79)	
Test statistic	-2.73	
Final Analysis, n	266	272
$\geq 10\%$ weight gain, n (%) ^d	47 (17.8)	81 (29.8)
$< 10\%$ weight gain, n (%) ^d	219 (82.2)	191 (70.2)
Risk difference vs olanzapine ^b , %	-13.7	
95% CI ^b	(-22.8, -4.6)	
Odds ratio for $\geq 10\%$ weight gain vs olanzapine ^b	0.50	
95% CI ^b	(0.31, 0.80)	
Adjusted test statistic ^c	-2.94	
Adjusted <i>P</i> value ^c	0.003	
NNT	7.29	
Proportions of patients with $\geq 7\%$ weight gain		
$\geq 7\%$ weight gain, n (%) ^d	73 (27.5)	116 (42.7)
$< 7\%$ weight gain, n (%) ^d	193 (72.5)	156 (57.3)
Risk difference vs olanzapine ^b , %	-15.9	
95% CI ^b	(-25.3, -6.5)	
Odds ratio for $\geq 7\%$ weight gain vs olanzapine ^b	0.50	
95% CI ^b	(0.33, 0.76)	
<i>P</i> value vs olanzapine	0.001	
NNT	6.29	

Percent change from baseline in body weight at week 24 was analyzed via analysis of covariance (ANCOVA). The model includes the treatment, race (black or African American, non-black or non-African American), and age group (< 30 years, ≥ 30 years) as factors and the baseline body weight as the covariate. Proportions of patients with $\geq 10\%$ and $\geq 7\%$ weight gain at week 24 were analyzed based on the logistic regression model adjusting for the same factors and covariate. Missing postbaseline assessments were imputed using multiple imputation method.

Baseline was defined as the last non-missing value before the first dose of study drug.

CI, confidence interval; LS, least squares; LSMD, least squares mean difference; MI, multiple imputation; NNT, number needed to treat; OLZ/SAM, combination of olanzapine and samidorphan; SD, standard deviation; SE, standard error.

^aRubin's rule was used to combine results from 500 imputed datasets.

^bRubin's rule was used to combine results from applying the ANCOVA model or logistic regression on 500 imputed datasets.

^cCui, Hung, and Wang (CHW) method was used to adjust for the unblinded interim analysis for sample size re-estimation. ^dNumber of responders and proportion were the mean number of responders and mean proportion from 500 imputed datasets, respectively. The mean number of responders was rounded to the nearest integer.

Statistics

Primary Analysis of Co-primary and Key Secondary Endpoints

The co-primary endpoint of percent change in body weight was analyzed by analysis of covariance (ANCOVA) with the multiple imputation (MI) method for handling of missing values. Only the on-treatment measurements were included in the analysis. The following steps were performed:

1. The missing data on body weight in stage 1 subjects (ie, first 200 subjects who were included in interim analysis) were imputed using MI. For any subject whose missing data pattern was non-monotonic (defined as having missing data in between visits), the Markov chain Monte Carlo method was used to impute the data to a monotonic missing pattern. Next, the missing data were imputed sequentially by each visit using a regression method. The imputation regression model included treatment group, race (black or African American, non-black or non-African American) and baseline age (<30, ≥30 years) as factors, and body weight at all previous visits (including baseline weight) as covariates.
2. Percent change from baseline in weight at week 24 of each of these multiply imputed datasets was analyzed by the ANCOVA model with treatment group, race (black or African American, non-black or non-African American), and baseline age (<30, ≥30 years) as factors, and the baseline weight as covariate.
3. Results from step 2 were combined using Rubin's method to get the stage 1 results, including estimated treatment effect, standard error (SE), and test statistic z_1 .
4. Steps 1 to 3 were repeated for stage 2 subjects (ie, subjects not included in the interim analysis). Estimated treatment effect, SE, and test statistic z_2 were obtained.
5. To adjust for the interim analysis for sample size re-estimation, the independent test statistics from 2 stages were combined using the CHW method with a fixed weight of $\sqrt{0.5}$ based on the original sample size.

In addition, to estimate the treatment effect, the same MI procedure was performed based on the entire dataset including all subjects.

Proportion of subjects with ≥10% and ≥7% weight gain at week 24 was derived based on the same complete datasets obtained from the MI procedure. The logistic regression model included the treatment group, race (black or African American, non-black or non-African American), and age (<30, ≥30 years) as factors, and the baseline weight as covariate. For subjects who prematurely discontinued the study drug but came back for weight assessments, only on-treatment weight assessments were included in the primary analyses.

Sensitivity Analysis of Co-primary and Key Secondary Endpoints

To assess the impact of missing data on the percent change in body weight at week 24, a descriptive evaluation of weight trajectories of subjects who completed the study relative to those who discontinued early was conducted. In general, weight gain profiles

for patients who discontinued OLZ/SAM prematurely were similar to weight gain profiles for those who completed the 24-week treatment period. Conversely, patients who discontinued olanzapine treatment early generally had greater weight gain and steeper weight gain trajectories vs those completing treatment (**Figure S2**).

To assess the robustness of the primary analyses, the following sensitivity analyses were further performed. The results (**Figure S3**) were consistent with the primary analyses presented in the main text.

- To assess the potential impact of missing data due to missing not at random (MNAR), the delta-adjusted pattern mixture model was conducted. It incorporated the clinical assumption that olanzapine subjects who discontinued at a given time point would have, on average, their unobserved weight gain decreased by some amount δ compared with the observed weight gain of subjects on the olanzapine arm who continued to the next time point. Subjects who discontinued from the OLZ/SAM arm would have the same weight gain trajectory as the OLZ/SAM subjects who stayed on the study. A sequential regression-based MI procedure was used to incorporate the assumption and to allow uncertainty in the imputations to be reflected appropriately in the analysis. The imputation model included the measurement at the current time point as the response variable, and the measurements at the previous time points, the baseline assessment, race (black or African American, non-black or non-African American), and age (<30, \geq 30 years) as covariates.
- To further assess the potential impact of missing data due to MNAR, the primary analyses were repeated including both on-treatment and off-treatment weight assessments after premature discontinuation of study drug.

Percent change from baseline in body weight was also analyzed by the mixed-effects with repeated measurements (MMRM) model, which included treatment, visit, treatment-by-visit interaction term, race (black or African American, non-black or non-African American), and age (<30, \geq 30 years) as categorical fixed effects; baseline weight was included as a covariate. An unstructured covariance structure was applied. Kenward-Roger approximation was used to adjust the denominator degree of freedom. The analysis was performed on all observed post-randomization on-treatment weight measurements without imputation of missing data.

The distribution of percent change from baseline in body weight at week 24 based on observed cases was further compared between OLZ/SAM and olanzapine by Wilcoxon rank-sum test.