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Supplementary Material

Article Title: Olanzapine/Samidorphan in Young Adults With Schizophrenia, Schizophreniform Disorder, or Bipolar I Disorder Who Are Early in Their Illness: Results of the Randomized, Controlled ENLIGHTEN-Early Study

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List of Supplementary Material for the article

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SUPPLEMENTARY MATERIAL

Appendix 1. Statistical Methods

Sample Size Determination

The target sample size was 200 patients per treatment group. This sample size was estimated to provide ≥90% power to detect significant differences in mean percent change in body weight relative to olanzapine at a 2-sided significance level of 0.05, assuming 5% and 8.5% weight gains at week 12 in the OLZ/SAM and olanzapine groups, respectively, based on previous findings,[1-3] with a common SD of 8% and a cumulative dropout rate of 35%.

Subgroup Analyses

Subgroup analyses of the percent changes from baseline in body weight at week 12 were performed for each of the following categories: diagnosis (schizophrenia/schizophreniform disorder vs BD-I), sex (male vs female), age (<30 vs ≥30 years), race (Black or African American vs non-Black or non-African American), baseline BMI (<25 vs ≥25 kg/m^2), and region (US- vs non-US regions). Subgroups were not powered for comparison between treatment groups.

A forest plot of the estimated treatment effect with 95% CIs was generated by subgroup; analyses were descriptive only.

Completer Analysis

An analysis of percent changes in body weight from baseline in study completers versus patients who discontinued early was performed using observed data. Patients who discontinued early were grouped by time of last weight assessment, and for each group, mean percent change from baseline in body weight at each visit was determined. Mean percent change from baseline in body weight was plotted over time for each discontinuation group and for study completers in the OLZ/SAM and olanzapine treatment groups separately.

Supplementary Table 1. Dosing Schedule[a]

Study Week	Dose, mg	
	OLZ/SAM (n=211)	**Olanzapine (n=215)**
Week 1	5/10, 10/10, 15/10, or 20/10	5, 10, 15, or 20
Week 2, by starting dose		
5 mg olanzapine 5/10 mg OLZ/SAM	10/10	10
10, 15, or 20 mg olanzapine 10/10, 15/10, or 20/10 mg OLZ/SAM	10/10, 15/10, or 20/10	10, 15, or 20
Week 3 through end of study	5/10, 10/10, 15/10, or 20/10	5, 10, 15, or 20

[a]Dosing changes were made at the discretion of the investigator, at on-site visits only; frequent adjustments were discouraged.

Abbreviations: OLZ/SAM, olanzapine combined with samidorphan.

Supplementary Table 2. Most Common Concomitant Medications in the Double-Blind Treatment Period (≥5% of Patients in Either Treatment Group)

Medication	**OLZ/SAM (n=211)**	**Olanzapine (n=215)**
Any concomitant medication**, n (%)**	113 (53.6)	108 (50.2)
Lorazepam	24 (11.4)	29 (13.5)
Risperidone	27 (12.8)	22 (10.2)
Zolpidem	14 (6.6)	13 (6.0)
Olanzapine	12 (5.7)	12 (5.6)
Benztropine mesylate	9 (4.3)	14 (6.5)

Abbreviations: OLZ/SAM, olanzapine combined with samidorphan.

Supplementary Table 3. Summary of Primary and Secondary Endpoints

Endpoint, Week 12	OLZ/SAM (n=202)	Olanzapine (n=206)
Body weight, LSM (SE) percent change from baseline	4.91 (0.60)	6.77 (0.60)
LSM (SE) difference vs olanzapine	−1.87 (0.75)	
95% CI of LSM difference	−3.33, −0.41	
P value	0.012	
Proportion with weight gain ≥10%, n (%)	44 (21.9)	63 (30.4)
OR vs olanzapine (95% CI)	0.64 (0.39, 1.05)	
P value[a]	0.075	
NNT	12	
Proportion with weight gain ≥7%, n (%)	67 (33.1)	92 (44.8)
OR vs olanzapine (95% CI)	0.61 (0.39, 0.94)	
NNT	9	
Waist circumference, LSM (SE) change from baseline, cm	2.99 (0.46)	3.90 (0.48)
LSM (SE) difference vs olanzapine	−0.92 (0.58)	
95% CI of LSM difference	−2.06, 0.22	
CGI-S total score, LSM (SE) change from baseline	−0.82 (0.060)	−0.73 (0.061)

[a]Secondary endpoints were analyzed using a hierarchical testing procedure. Because there was no statistically significant difference between treatment groups for ≥10% weight gain, *P* values are not reported for the remaining secondary endpoints.

Abbreviations: LSM, least-squares mean; NNT, number needed to treat; OLZ/SAM, olanzapine combined with samidorphan; OR, odds ratio.

Supplementary Table 4. Serious Adverse Events[a]

Preferred Term	OLZ/SAM (n=211), n (%)	Olanzapine (n=215), n (%)
Any serious AE	8 (3.8)	8 (3.7)
Schizophrenia	3 (1.4)	2 (0.9)
Limb deformity	1 (0.5)	0
Seizure	1 (0.5)	0
Suicidal ideation	1 (0.5)	0
Toxicity to various agents[b]	1 (0.5)	0
Varicella	1 (0.5)	0
Anxiety	0	2 (0.9)
Acute respiratory failure	0	1 (0.5)
Bipolar I disorder	0	1 (0.5)
Drug abuse	0	1 (0.5)
Intentional overdose	0	2 (0.9)
Psychotic disorder	0	1 (0.5)

[a]One patient assigned to olanzapine who discontinued due to an AE before receiving study drug is excluded from this table.
[b]Fatal outcome; occurred during the safety follow-up period.

Abbreviations: AE, adverse event; OLZ/SAM, olanzapine combined with samidorphan.

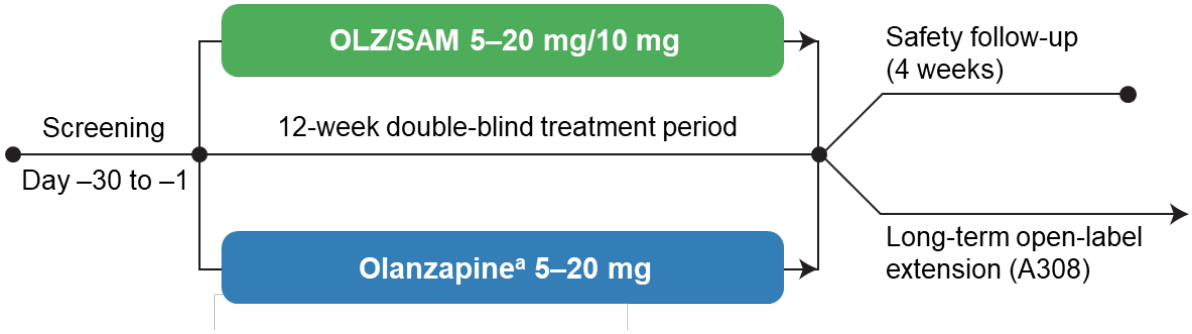
Supplementary Table 5. Select Potentially Clinically Significant Laboratory Parameters

Lab Parameter/Criterion	**OLZ/SAM (n=211), n/m (%)**	**Olanzapine (n=215), n/m (%)**
ALT ≥3 × ULN	16/192 (8.3)	13/196 (6.6)
AST ≥3 × ULN	5/198 (2.5)	3/200 (1.5)
Bilirubin, total ≥2.0 mg/dL	0/196	0/201
Creatine kinase ≥3 × ULN	10/186 (5.4)	11/194 (5.7)
Glucose, fasting		
<50 mg/dL	1/180 (0.6)	0/186
≥126 mg/dL	10/180 (5.6)	2/186 (1.1)
HbA1c (normal to ≥5.7%)	29/174 (16.7)	19/173 (11.0)
Prolactin		
>3 × ULN (female)	4/57 (7.0)	1/59 (1.7)
>3 × ULN (male)	0/122	3/127 (2.4)
Total cholesterol, fasting ≥240 mg/dL	13/174 (7.5)	14/175 (8.0)
HDL, fasting ≤40 mg/dL	27/153 (17.6)	25/152 (16.4)
LDL, fasting ≥160 mg/dL	22/166 (13.3)	20/164 (12.2)

Triglycerides, fasting ≥200 mg/dL	25/167 (15.0)	29/176 (16.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; m, number of patients who did not have a potentially clinically significant value at baseline and had ≥1 postbaseline assessment; n, number of patients who did not have a potentially clinically significant value at baseline and met the criteria postbaseline during the double-blind treatment period; OLZ/SAM, olanzapine combined with samidorphan; ULN, upper limit of normal.

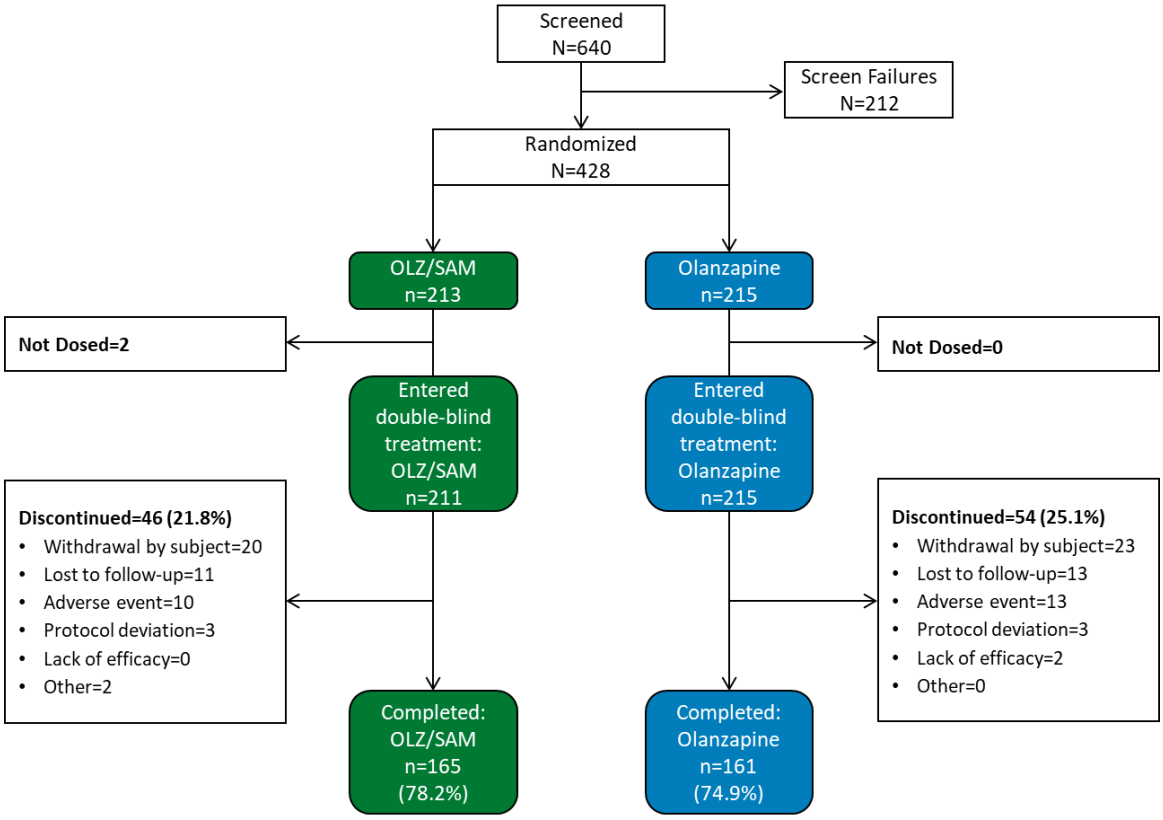
Supplementary Figure 1. Study Design



[a]Initial olanzapine dose was 5 mg in both groups; titration as per investigator, with flexible dosing at 5-mg intervals throughout.

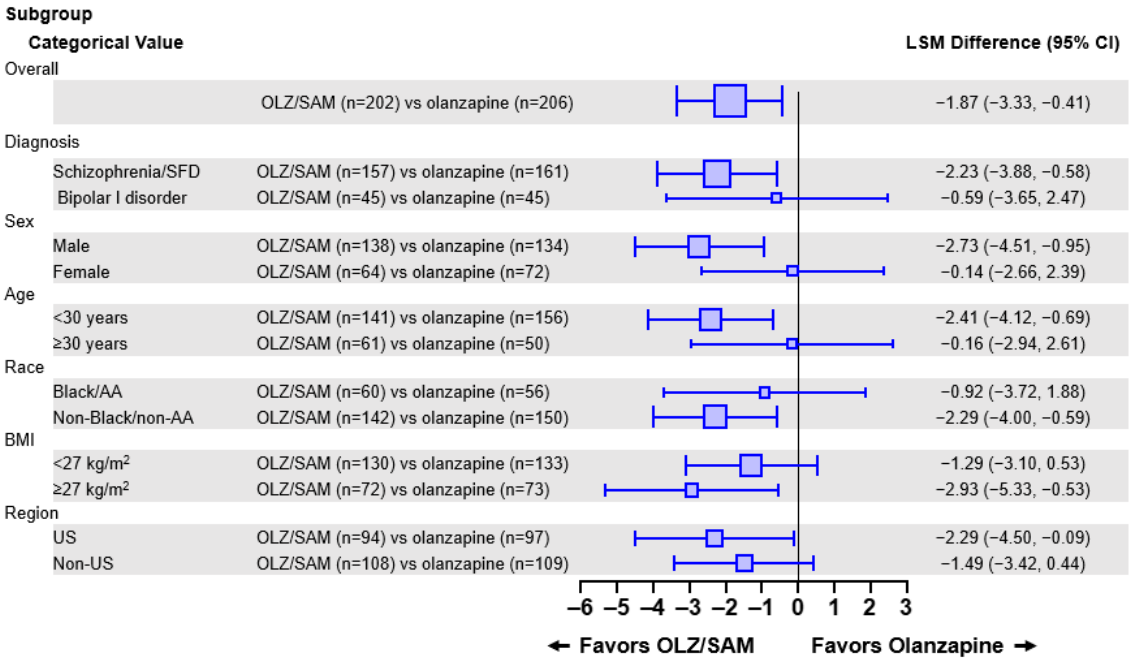
Abbreviations: OLZ/SAM, olanzapine combined with samidorphan.

Supplementary Figure 2. Patient Disposition



Abbreviations: OLZ/SAM, olanzapine combined with samidorphan.

Supplementary Figure 3. Forest Plot of Percent Changes From Baseline in Body Weight at Week 12 by Subgroup[a,b]

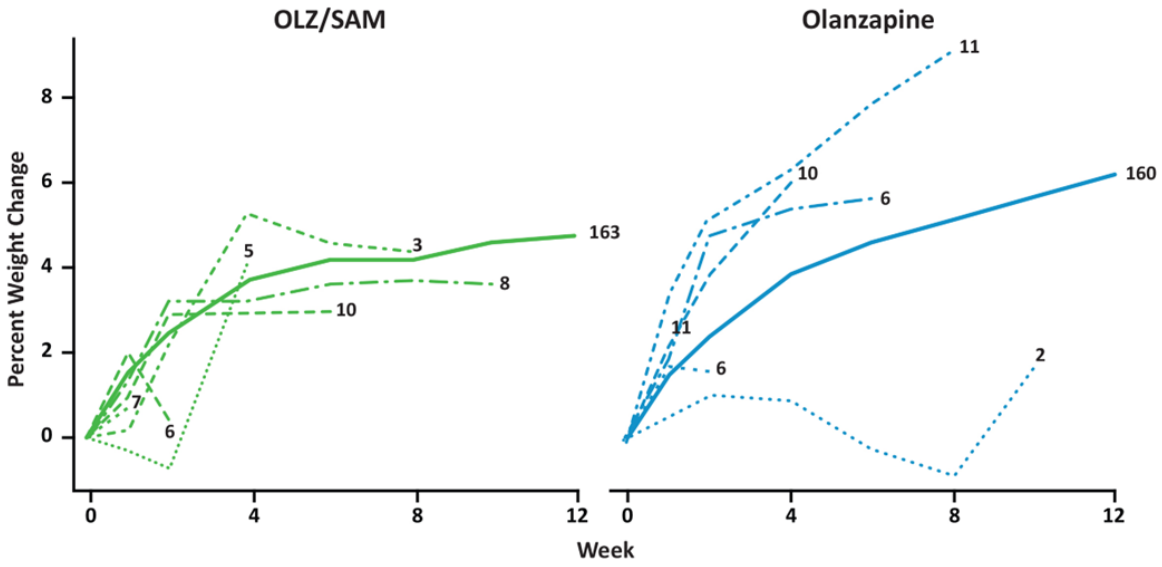


[a]Forest plot marker size is proportional to group n.

[b]Analyses were conducted using analysis of covariance with multiple imputation for missing postbaseline data. Subgroup analyses were not powered for comparison between treatment groups.

Abbreviations: AA, African American; BMI, body mass index; LSM, least-squares mean; OLZ/SAM, combination of olanzapine and samidorphan; SFD, schizophreniform disorder.

Supplementary Figure 4. Percent Changes From Baseline in Body Weight by Treatment for Patients Discontinuing and for Those Completing the Study



Solid lines denote the mean over time for patients who completed the study; dashed lines denote the mean over time for patients who discontinued prematurely at given visits, grouped by the time of patients' last weight assessment. The number of patients in each group is indicated at the right of each curve.

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