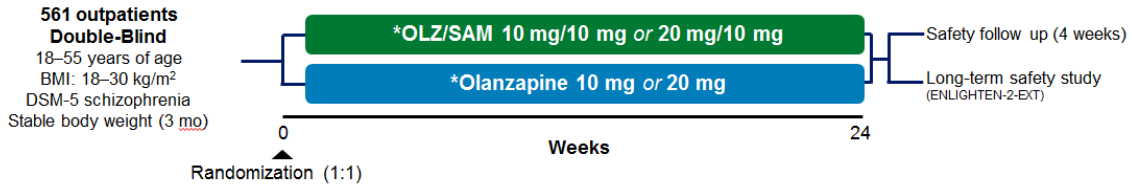
Data supplement for Correll et al., Effects of Olanzapine Combined With Samidorphan on Weight Gain in Schizophrenia: A 24-Week Phase 3 Study. Am J Psychiatry (doi: 10.1176/appi.ajp.2020.19121279)

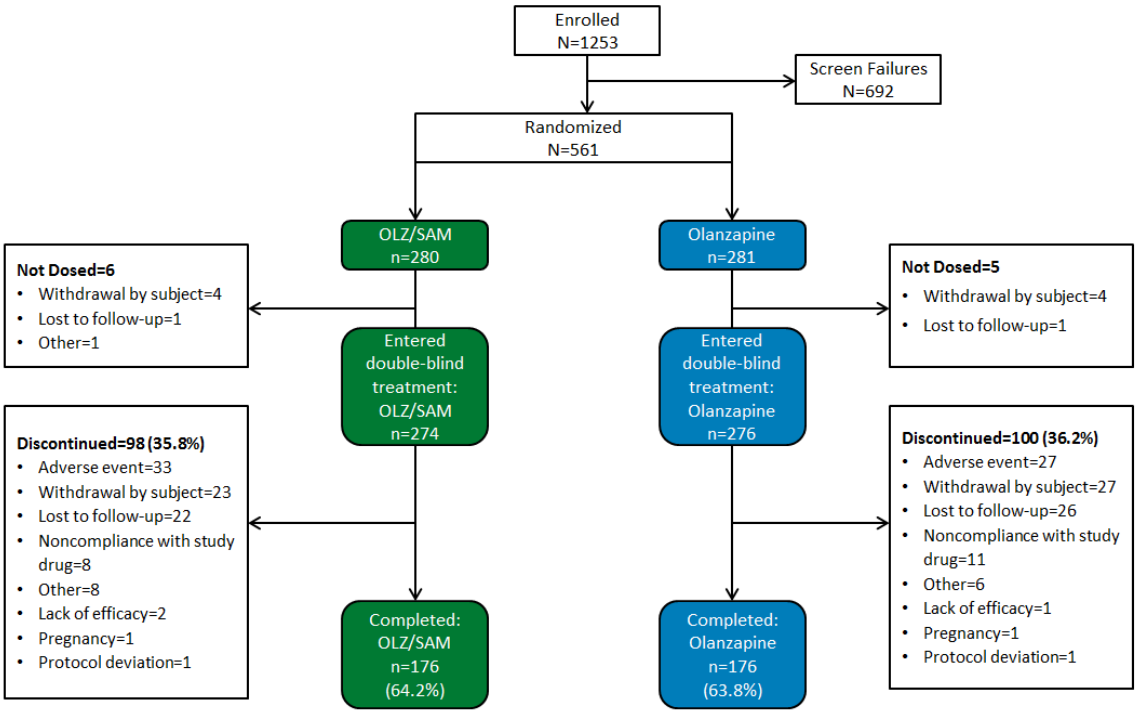
# CONTENTS

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

**A**



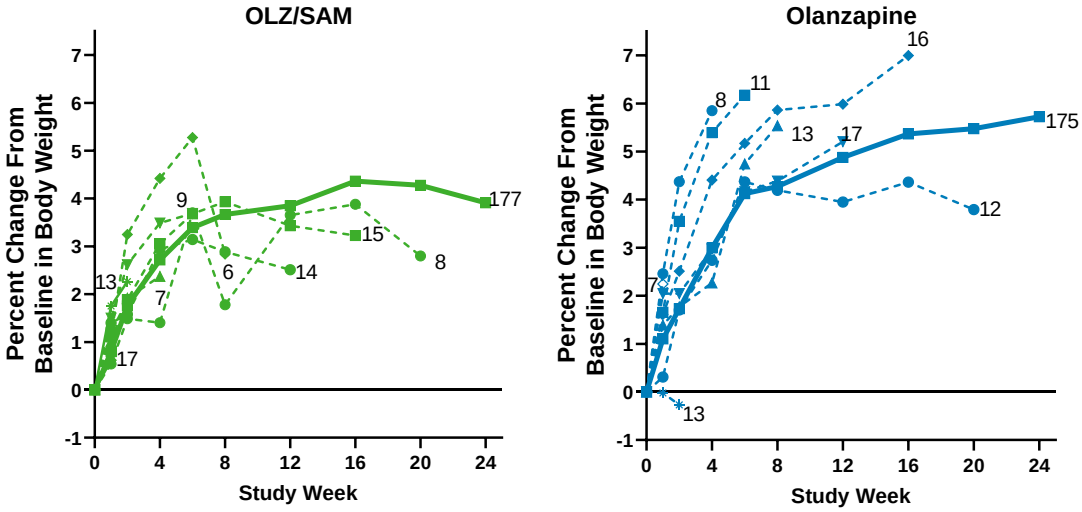

**B**




*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.

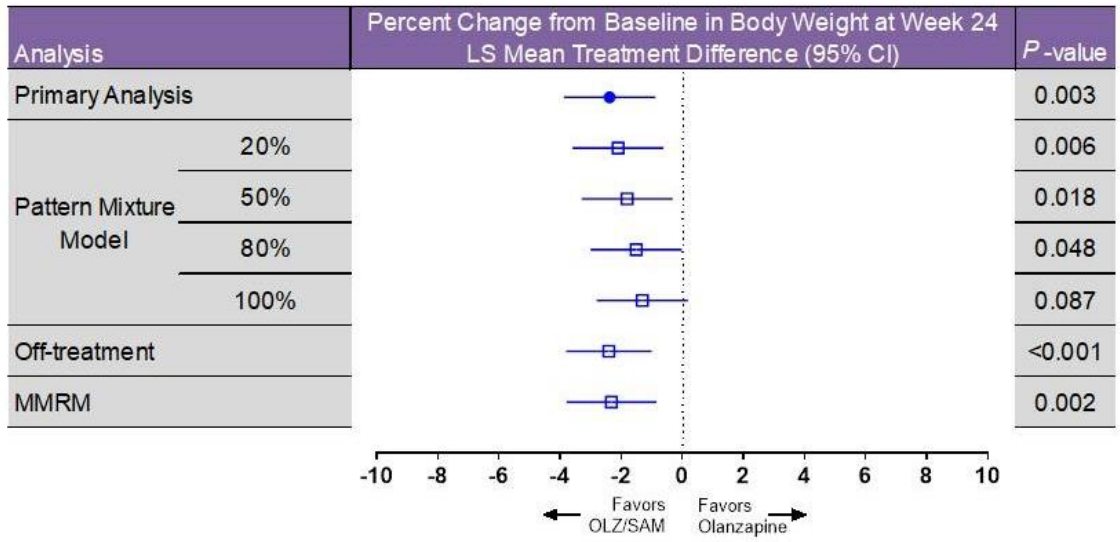
**Figure S2. Weight gain trajectory in patients with early discontinuation vs patients who completed the study**



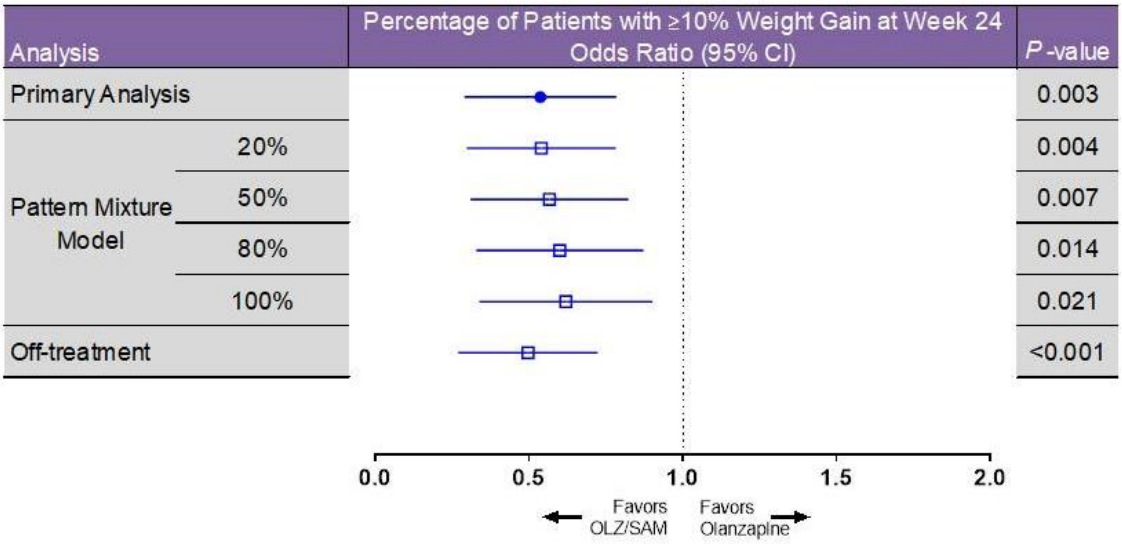

Solid lines denote the weight gain curve of patients who completed the study. Dashed lines denote patients who prematurely discontinued at given visits. Numbers of patients summarized by each curve are noted. In the OLZ/SAM group, weight gain profiles of discontinuing patients were not much different 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 (≥10%)**

A

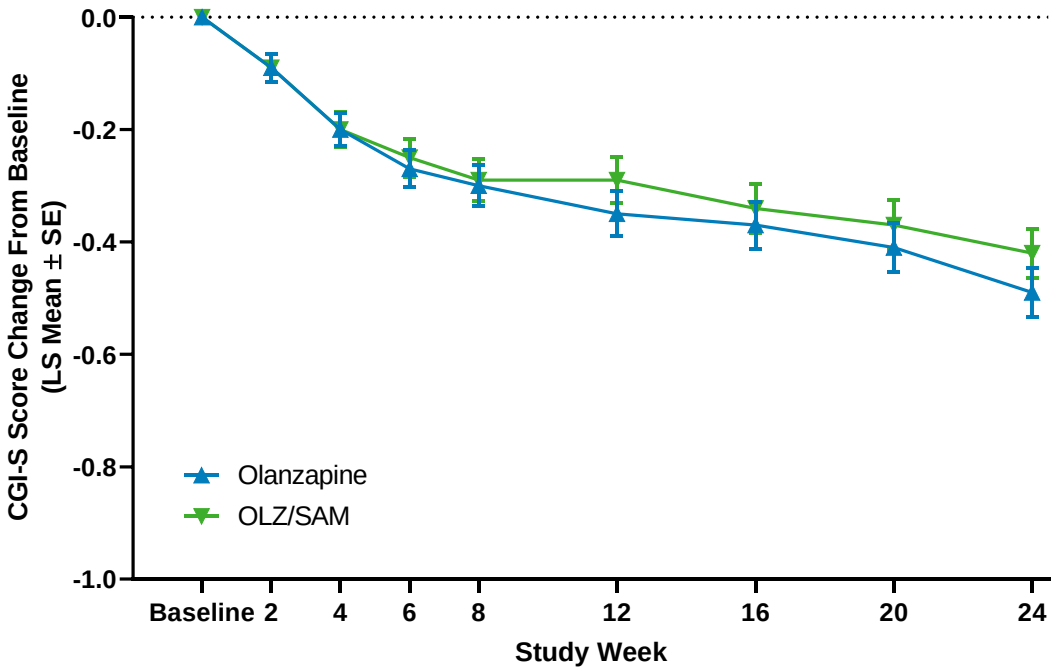



B




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.
[a]Mean (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 ± SD, kg | 77.98 ± 13.69 | 76.76 ± 13.36 |
| Week 24, mean ± SD, kg[a] | 80.95 ± 15.45 | 81.26 ± 15.42 |
| Percent change from baseline body weight at week 24 | | |
| Mean ± SD[a] | 3.87 ± 8.63 | 5.84 ± 7.59 |
| LS mean ± SE[b] | 3.08 ± 1.17 | 4.91 ± 1.22 |
| 95% CI[b] | (0.79, 5.36) | (2.51, 7.31) |
| LSMD ± SE vs olanzapine[b] | –1.83 ± 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 ± SD, kg | 76.43 ± 13.69 | 77.86 ± 13.57 |
| Week 24, mean ± SD, kg[a] | 78.88 ± 14.12 | 82.54 ± 15.23 |
| Percent change from baseline body weight at week 24 | | |
| Mean ± SD[a] | 3.47 ± 7.31 | 6.15 ± 8.49 |
| LS mean ± SE[b] | 4.70 ± 0.85 | 7.42 ± 0.79 |
| 95% CI[b] | (3.04, 6.36) | (5.87, 8.96) |
| LSMD ± SE vs olanzapine[b] | –2.72 ± 0.95 | |
| 95% CI[b] | (–4.58, –0.85) | |
| Test statistic[c] | –2.86 | |
| Final analysis, n | 266 | 272 |
| Baseline, mean ± SD, kg | 77.00 ± 13.68 | 77.45 ± 13.48 |
| Week 24, mean ± SD, kg[a] | 79.67 ± 14.64 | 82.02 ± 15.24 |
| Mean change from baseline to week 24 ± SE, kg[a] | 3.18 ± 0.52 | 5.08 ± 0.50 |
| Percent change from baseline body weight at week 24 | | |
| Mean ± SD[a] | 3.65 ± 7.79 | 6.00 ± 8.14 |
| LS mean ± SE[b] | 4.21 ± 0.68 | 6.59 ± 0.67 |
| 95% CI[b] | (2.88, 5.6) | (5.28, 7.90) |
| LSMD ± SE vs olanzapine[b] | –2.38 ± 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 ≥10% weight gain** | | |
| Stage 1 subjects (before interim analysis), n | 98 | 102 |
| ≥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 ≥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 |
| ≥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 ≥10% weight gain vs olanzapine[b] | 0.43 | |
| 95% CI[b] | (0.24, 0.79) | |
| Test statistic | –2.73 | |
| Final Analysis, n | 266 | 272 |
| ≥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 ≥10% weight gain vs olanzapine[b] | 0.50 | |
| 95% CI[b] | (0.31, 0.80) | |
| Adjusted test statistic[c] | –2.94 | |
| Adjusted *P* value[c] | 0.003 | |
| NNT | 7.29 | |
| **Proportions of patients with ≥7% weight gain** | | |
| ≥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 ≥7% weight gain vs olanzapine[b] | 0.50 | |
| 95% CI[b] | (0.33, 0.76) | |
| *P* 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 ≥10% and ≥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.

[a]Rubin's rule was used to combine results from 500 imputed datasets.

[b]Rubin's rule was used to combine results from applying the ANCOVA model or logistic regression on 500 imputed datasets.

[c]Cui, Hung, and Wang (CHW) method was used to adjust for the unblinded interim analysis for sample size re-estimation. [d]Number 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 $z1$.
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 $z2$ 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, ≥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, ≥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.