



A phase 3, multicenter study to assess the 1-year safety and tolerability of a combination of olanzapine and samidorphan in patients with schizophrenia: Results from the ENLIGHTEN-2 long-term extension

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ABSTRACT

Aim: A combination of olanzapine and samidorphan (OLZ/SAM) is in development for the treatment of patients with schizophrenia or bipolar I disorder and is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. This 52-week open-label extension (NCT02873208; ENLIGHTEN-2-EXT) assessed the long-term safety and tolerability of OLZ/SAM in patients with schizophrenia.

Methods: Patients completing the 24-week randomized, double-blind, phase 3 ENLIGHTEN-2 study (NCT02694328) comparing weight change from baseline to week 24 with OLZ/SAM versus olanzapine were eligible to enroll in the 52-week ENLIGHTEN-2-EXT study. Assessments included adverse events (AEs; each visit), weight/waist circumference (every other week for the first 8 weeks, then every 4 weeks thereafter), metabolic laboratory parameters (weeks 4, 12, 24, 36, and 52), Positive and Negative Syndrome Scale (PANSS) scores (weeks 2, 4, 8, 12, 24, 36, and 52), and Clinical Global Impression-Severity (CGI-S) scores (weeks 2 and 4, then every 4 weeks thereafter through week 48, and at week 52). Analyses were based on observed results using descriptive statistics. Baseline was relative to the first OLZ/SAM dose in the extension study.

Results: In total, 265 patients were enrolled and received at least 1 dose of OLZ/SAM; 167 (63.0%) completed the 52-week extension study. Common AEs ($\geq 5\%$) were weight decreased ($n = 23$; 8.7%), extra dose administered ($n = 21$; 7.9%), headache ($n = 18$; 6.8%), and weight increased ($n = 16$; 6.0%). At week 52, the mean (SD) change from baseline for weight and waist circumference was -0.03 (6.17) kg and -0.35 (6.12) cm, respectively. Changes in fasting lipid and glycemic parameters were generally small and remained stable over 52 weeks. During the extension, PANSS total scores remained stable, and at week 52, 81.3% of patients had CGI-S scores of 3 or less, reflecting mild illness severity.

Conclusions: OLZ/SAM was generally well tolerated over 52 weeks. Weight, waist circumference, metabolic laboratory parameters, and schizophrenia symptoms remained stable throughout the study.

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1. Introduction

Olanzapine is a second-generation antipsychotic treatment with established efficacy in both schizophrenia and bipolar I disorder (Cipriani et al., 2011; Kishimoto et al., 2019; Lieberman et al., 2005; Yildiz et al., 2015). In schizophrenia, meta-analyses indicate that olanzapine is one of the most effective antipsychotics, both for acute as well as maintenance treatment (Kishimoto et al., 2019; Leucht et al., 2013). Olanzapine is also effective in the treatment of manic or

mixed episodes associated with bipolar I disorder, for which it is indicated either as monotherapy or as an adjunct to lithium or valproate, and for maintenance treatment (Cipriani et al., 2011; Yildiz et al., 2015). However, treatment with olanzapine is associated with an increased risk of substantial weight gain and metabolic dysregulation, including the development of diabetes and dyslipidemia (Baker et al., 2009; Gianfrancesco et al., 2002; Koro et al., 2002; Leucht et al., 2013; Lieberman et al., 2005), which has limited its clinical utility (Berkowitz et al., 2012).

A combination of olanzapine and samidorphan (OLZ/SAM) is currently in development for the treatment of patients with schizophrenia or bipolar I disorder, and is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain.

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Although the precise mechanism of action of samidorphan in the mitigation of olanzapine-associated weight gain is not known, its effects are hypothesized to occur through both central and peripheral antagonism (Shram et al., 2015) of the endogenous opioid system (Cunningham et al., 2019), which is involved in the regulation of weight and metabolism (Czyzyk et al., 2010; Czyzyk et al., 2012; Tabarin et al., 2005). While mitigation of olanzapine-associated weight gain has been observed in multiple preclinical and clinical studies with OLZ/SAM (Correll et al., 2020; Cunningham et al., 2019; Martin et al., 2019), samidorphan does not appear to affect body weight as a monotherapy (Silverman et al., 2018). Previously reported phase 2 and 3 studies in adults with schizophrenia have established that OLZ/SAM treatment results in meaningful improvements in symptoms of schizophrenia, and these improvements are similar to those observed with olanzapine (Correll et al., 2020; Martin et al., 2019; Potkin et al., 2020). Additionally, in the ENLIGHTEN-2 study ($N = 561$; [ClinicalTrials.gov](#) identifier: NCT02694328), treatment with OLZ/SAM resulted in significantly less weight gain at 24 weeks compared with olanzapine. Furthermore, the likelihood of patients gaining at least 7% or 10% or more of their baseline body weight was reduced by half with OLZ/SAM compared with olanzapine (Correll et al., 2020). Here, results from the ENLIGHTEN-2 extension (ENLIGHTEN-2-EXT; [ClinicalTrials.gov](#) identifier: NCT02873208) are described. This 52-week study was conducted to further characterize the long-term safety and tolerability of OLZ/SAM in adults with schizophrenia.

2. Methods

Patients who completed the ENLIGHTEN-2 study (Correll et al., 2020) were eligible for enrollment in this phase 3, multicenter, 52-week, open-label extension study. The ENLIGHTEN-2-EXT was conducted between August 2016 and October 2019 at 45 sites in the United States in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Institutional review boards for each investigational site approved the study protocol and its amendments. All patients provided written informed consent.

2.1. Study design and treatment

The first study visit occurred within 7 days of completion of ENLIGHTEN-2 (Correll et al., 2020). Patients entering the extension received open-label OLZ/SAM at the equivalent olanzapine dose administered at the end of ENLIGHTEN-2 (Fig. 1) (Correll et al., 2020). For example, patients taking 20 mg olanzapine at the end of ENLIGHTEN-2 (either as olanzapine 20 mg or as OLZ/SAM 20 mg/10 mg [20/10]) were started on OLZ/SAM 20/10 mg at the beginning of this extension study. Dose changes were allowed during study site visits at the discretion of the investigator, but frequent dose changes were discouraged. Over the course of the 52-week study, OLZ/SAM was administered at daily doses of 10 mg/10 mg (10/10), 15 mg/10 mg (15/10), or 20/10 mg.

Study visits occurred every other week through 52 weeks of treatment. Patients completing the 52-week extension were eligible to enter an open-label, follow-up extension, where they could receive OLZ/SAM treatment for up to 4 additional years ([ClinicalTrials.gov](#) identifier: NCT03201757). Patients who opted not to continue in the 4-year follow-up study entered a 4-week safety follow-up period.

2.2. Study participants

Interested patients who completed the 24-week treatment period of ENLIGHTEN-2 were eligible for participation in the ENLIGHTEN-2-EXT if they had the potential to benefit from treatment with OLZ/SAM (based on antipsychotic efficacy and tolerability, in the clinical judgment of the investigator), and had provided consent and agreed to follow study procedures. Enrollment criteria for ENLIGHTEN-2 were previously published (Correll et al., 2020). Briefly, ENLIGHTEN-2 enrolled patients who were 18 to 55 years of age, had a primary diagnosis of schizophrenia, and had a baseline body mass index between 18 and 30. Patients were excluded from ENLIGHTEN-2 if less than 1 year had passed since the initial onset of active-phase schizophrenia symptoms, if they were antipsychotic naive, if antipsychotic medication had been initiated less than a year before that study, or if there was a history of treatment-resistant schizophrenia. Patients were also excluded if they had any clinically significant or unstable medical illness that might affect efficacy or safety during the study, clinically significant hypotension or hypertension not stabilized by medical therapy, unstable thyroid dysfunction in the last 6 months, any gastrointestinal surgical procedures within the preceding year, any surgical procedure for weight loss, or plans for liposuction during the study. Opioid agonists and antagonists, olanzapine (within 60 days prior to screening), and weight loss or hypoglycemic agents were excluded treatments. Medications contraindicated with olanzapine use or those exhibiting drug-interaction potential with olanzapine were also prohibited. Patients using statins were required to enter on a stable dose (no dose within 3 months prior to randomization). Key exclusion criteria for ENLIGHTEN-2-EXT included the use of medications contraindicated with olanzapine or with known drug-interaction potential, use of prohibited drugs identified through a urine drug test, and females who were pregnant or nursing.

2.3. Assessments

Safety and tolerability evaluations included adverse event (AE) monitoring, weight and waist circumference measurements, clinical laboratory testing, vital signs, 12-lead electrocardiograms (ECGs), and movement disorder rating scales (Abnormal Involuntary Movement Scale [AIMS] (Guy, 1976), Barnes Akathisia Rating Scale [BARS] (Barnes, 1989), and Simpson-Angus Scale [SAS] (Simpson and Angus, 1970)). The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011) was utilized to characterize patients' suicidal ideation or behavior. Body weight measurements were made using the same scale and under consistent conditions at each assessment. Patients wore a

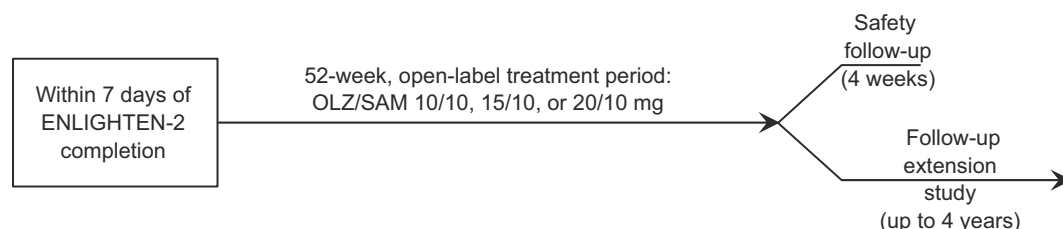


Fig. 1. Study design schematic. Stable outpatients entered this study within 7 days of completing the prior 24-week, double-blind weight efficacy study (ENLIGHTEN-2) (Correll et al., 2020). Initial OLZ/SAM doses were based on the olanzapine dose (10 or 20 mg) received at the conclusion of ENLIGHTEN-2; subsequently, the olanzapine dose in OLZ/SAM could be adjusted throughout the study period based on investigator discretion (the dose of samidorphan in OLZ/SAM was fixed at 10 mg). Prespecified visits occurred biweekly. After the 52-week treatment period, patients were monitored for an additional 4 weeks in a safety follow-up period or could continue receiving OLZ/SAM treatment in a long-term safety study. OLZ/SAM, combination of olanzapine and samidorphan.

hospital gown, removed all personal items (e.g., watches and jewelry), and were asked to void immediately prior to weight measurement. Body weight and waist circumference were measured in triplicate at each assessment, and the median of the 3 values was used. Patients were also asked to fast for at least 8 h before study visits when blood samples that included assessments of fasting cholesterol, triglycerides, glucose, and insulin were taken. Fasting status was self-reported, without independent confirmation. Supplemental Table S1 provides a schedule and timing of study assessments.

The long-term effects of OLZ/SAM treatment on psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impression-Severity (CGI-S) (Guy, 1976) scale. PANSS assessments were conducted at weeks 2, 4, 8, 12, 24, 36, and 52; the CGI-S was evaluated at weeks 2 and 4, every 4 weeks thereafter through week 48, and at week 52. The proportion of patients meeting CGI-S severity criteria by visit (normal to mildly ill: score ≤ 3 ; moderately ill: score of 4; markedly ill: score ≥ 5) was also assessed.

2.4. Statistical analyses

All patients who received at least 1 dose of OLZ/SAM were included in the safety analysis. Safety and efficacy outcomes were summarized descriptively based on observed data, without imputation for missing values. Baseline was relative to the first OLZ/SAM dose administered in this extension study (ENLIGHTEN-2-EXT).

The time to treatment discontinuation was estimated using the Kaplan-Meier method (Kaplan and Meier, 1958). For patients who discontinued prematurely, time to event was the time from the first to the last OLZ/SAM doses. All other patients were censored at the date of the last OLZ/SAM dose (Goel et al., 2010).

3. Results

In total, 266 patients who completed ENLIGHTEN-2 (75.6% of all completers) enrolled in ENLIGHTEN-2-EXT. Of these, 265 received at least 1 dose of OLZ/SAM and were included in the analysis (Table 1). Overall, 167 (63.0%) patients completed the treatment period (Fig. 2).

Patients were, on average, aged 40.7 years, with a mean weight at baseline of 80.6 kg. Patients had mild to moderate illness severity at the beginning of the study, based on mean PANSS and CGI-S scores at baseline (Table 1) (Leucht et al., 2005). Based on a post hoc analysis, demographic and baseline characteristics were similar between those who discontinued ($n = 98$) and those who completed the study ($n = 167$). This included similar proportions of male (70.4% vs 73.7%) and black participants (72.5% vs 69.5%) who discontinued versus completed, respectively. Additionally, mean age (39.3 vs 41.4 years), body weight

(80.2 vs 80.9 kg), and baseline PANSS total scores (59.5 vs 58.8) were comparable between study discontinuers and completers, respectively.

In this study, the mean (SD) olanzapine dose in OLZ/SAM was 17.8 mg/day. The most frequent olanzapine dose in OLZ/SAM (i.e., the mean modal dose) was 18.4 mg/day, with a majority of patients (83.7%) receiving 20/10 mg/day.

3.1. Safety

Adverse events were reported in 161 (60.8%) patients; a summary of AEs, including AEs that occurred in at least 2% of patients, is presented in Table 2. Most AEs were mild or moderate in severity; 7 (2.6%) patients experienced a severe AE. In total, 15 (5.7%) patients discontinued because of an AE; glycosylated hemoglobin increase ($n = 3$; 1.1%) and psychotic disorder ($n = 2$; 0.8%) were the only AEs that led to discontinuation in more than 1 patient. Note that, per protocol, patients were to be discontinued if they registered glycosylated hemoglobin (HbA1c) values of 6.5% or greater.

Seven serious AEs (SAEs) occurred in 5 (1.9%) patients. Two patients experienced an SAE of worsening or exacerbation of schizophrenia; 1 patient experienced 2 separate SAEs of psychotic disorder, with the second instance co-occurring with an SAE of agitation; 1 patient experienced SAEs of alcoholic gastritis and acute kidney injury; and 1 patient experienced an SAE of pulmonary embolism. Of these, only the SAE of pulmonary embolism was considered by the investigator to be related to study drug. Serious AEs (pulmonary embolism and psychotic disorder) led to study discontinuation for 2 patients. No deaths occurred during the study.

3.2. Body weight

Overall, weight remained stable in patients throughout the 52 weeks of treatment. The mean (SD) change in body weight from baseline to week 52 was -0.03 (6.22) kg (Fig. 3). The weight change profile observed with OLZ/SAM treatment at week 52 was similar regardless of the treatment received in the antecedent ENLIGHTEN-2 study (eg, OLZ/SAM or olanzapine; Supplemental Fig. 1). Consistent with the stability in body weight, small changes in body mass index (BMI) were observed for patients continuing treatment over 52 weeks (mean [SD] change from baseline to week 52, -0.03 [2.04] kg/m²). Change in BMI was 0.12 (2.02) kg/m² among patients who previously received OLZ/SAM, and -0.20 (2.06) kg/m² among those who previously received olanzapine. Over 52 weeks of treatment, 57/265 (21.5%) patients experienced clinically significant ($\geq 7\%$) weight gain at some point during the study. There were 56/265 (21.1%) patients who experienced clinically significant weight loss of at least 7%. The proportions of patients with clinically significant weight gain or weight loss were similar in patients who received olanzapine versus OLZ/SAM in the preceding ENLIGHTEN-2 study, and no trends in types or frequency of AEs were observed among patients reporting potentially clinically significant weight gain or loss.

3.3. Waist circumference

Waist circumference remained stable in patients throughout treatment. At week 52, the mean (SD) change in waist circumference among patients was -0.35 (6.12) cm (Fig. 4). The waist circumference change observed at week 52 was similar, regardless of the treatment received in the antecedent ENLIGHTEN-2 study (eg, OLZ/SAM or olanzapine; Supplemental Fig. 2).

3.4. Lipid and glycemic parameters

Fasting lipid and glycemic parameters remained stable with generally small mean changes observed over the course of the study. Table 3 depicts the mean change from baseline in fasting measures of

Table 1
Baseline demographics and disease characteristics.

Parameter	All patients ^a (N = 265)
Age, mean (SD), years	40.7 (9.7)
Males, n (%)	192 (72.5)
Race, n (%)	
Black	187 (70.6)
White	64 (24.2)
Multiple races	6 (2.3)
Other	3 (1.1)
Asian	3 (1.1)
American Indian or Alaska native	2 (0.8)
Weight, mean (SD), kg	80.6 (14.7)
BMI, mean (SD), kg/m ²	26.8 (3.8)
PANSS total score, mean (SD)	59.0 (11.8)
CGI-S score, mean (SD)	3.1 (0.7)

BMI, body mass index; CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale.

^a Patients who received at least 1 dose of OLZ/SAM.

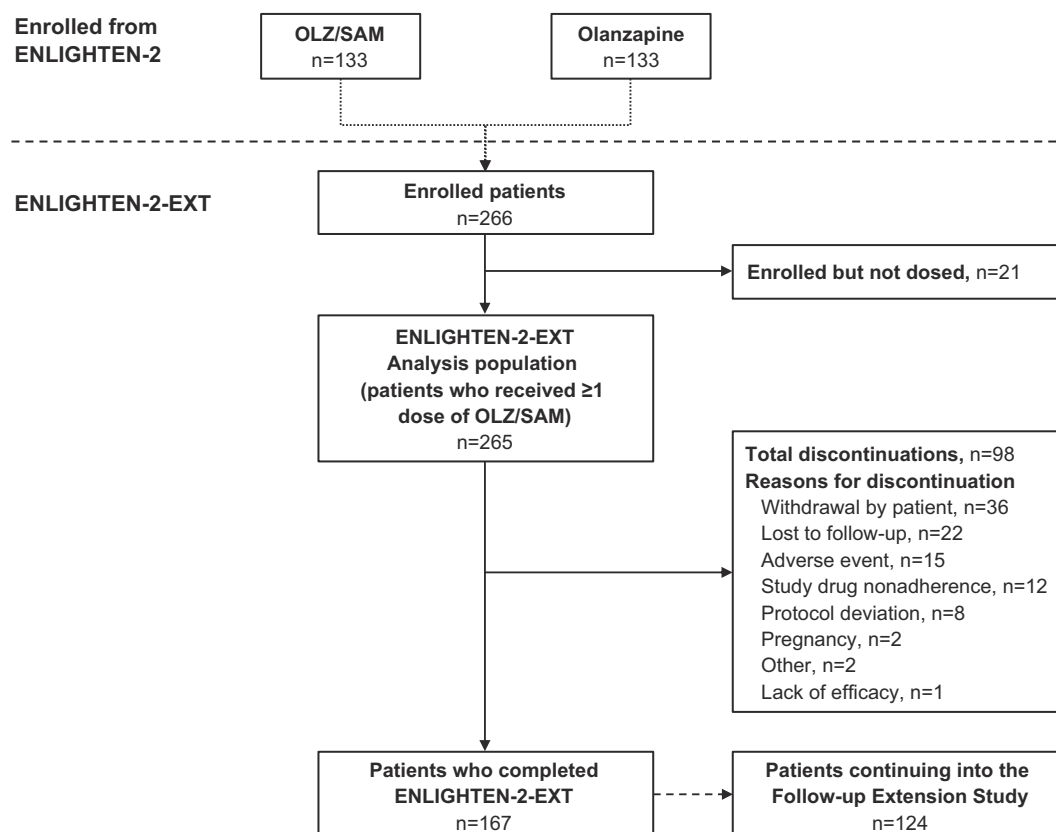


Fig. 2. Patient disposition. OLZ/SAM, combination of olanzapine and samidorphan.

total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, and insulin for patients at study completion, as well as other time points during treatment. HbA1c values also remained stable over 52 weeks.

Table 2
Adverse events summary (baseline to week 52).

Patients, n (%)	All patients ^a (N = 265)
Any AE	161 (60.8)
By highest severity	
Mild	93 (35.1)
Moderate	61 (23.0)
Severe	7 (2.6)
AE leading to treatment discontinuation ^b	15 (5.7)
AEs reported in ≥2% of patients	
Weight decreased	23 (8.7)
Extra dose administered ^c	21 (7.9)
Headache	18 (6.8)
Weight increased	16 (6.0)
Upper respiratory tract infection	12 (4.5)
Nasopharyngitis	10 (3.8)
Back pain	9 (3.4)
Blood creatine phosphokinase increased	8 (3.0)
Toothache	7 (2.6)
Hypertension	6 (2.3)
Nausea	6 (2.3)

AE, adverse event; GGT, gamma-glutamyltransferase; OLZ/SAM, combination of olanzapine and samidorphan.

^a Patients who received at least 1 dose of OLZ/SAM.

^b The AEs leading to discontinuation were blood prolactin increased, blood triglycerides increased, dizziness, electrocardiogram T wave abnormality, GGT increased, diabetes mellitus, nausea, pulmonary embolism, sedation, seizure, and somnolence ($n = 1$ each), psychotic disorder ($n = 2$) and glycosylated hemoglobin increased ($n = 3$).

^c In phase 3 studies, sites were requested to report any extra doses of study drug administered as AE (extra dose administered). These extra doses were accidentally taken by patients and were recorded for drug accountability reasons.

The proportion of patients experiencing sustained shifts in fasting lipid and glycemic parameters (ie, from normal or borderline values at baseline to high values on their last two on-treatment assessments) was substantially lower than the proportion of patients who experienced anytime shifts in these parameters (Table 4). For example, 29 patients (11.4%) experienced a shift in glucose values from <126 mg/dL to ≥ 126 mg/dL at any visit during the study, whereas 1 patient (0.4%) had a sustained shift in glucose values above this threshold. Anytime shifts in HbA1c values from normal to borderline (ie $\geq 5.7\%$ to $<6.5\%$) occurred in 49 patients (28.2%), but sustained shifts in HbA1c values higher than 5.7% were observed in 17 patients (11.0%). A total of 6 patients (2.3%), all with borderline values ($\geq 5.7\%$) at baseline, had shifts to high HbA1c values ($\geq 6.5\%$). No patient with a normal HbA1c value ($<5.7\%$) at baseline shifted to a high HbA1c value ($\geq 6.5\%$) during the study.

Four patients experienced lipid- or glucose-related AEs that led to treatment discontinuation. Three patients had increased HbA1c (values of at least 6.5%; a discontinuation criterion). Of these patients, 1 also experienced increased triglycerides and one patient developed diabetes mellitus. The patient who developed diabetes entered the extension after 6 months of exposure to OLZ/SAM with a fasting glucose concentration of 124 mg/dL, a borderline HbA1c value of 5.7%, and an insulin concentration of 16.1 μ U/mL. Following an additional 6 months of treatment during the extension study, the patient's weight and glycemic parameters increased further, leading to study discontinuation.

3.5. Clinical laboratory parameters and other safety measures

Mean changes from baseline to week 52 in serum chemistries, including liver and renal function parameters, hematology indices, vital signs, and ECGs were generally small and were not considered to be clinically meaningful (data not shown). The overall incidence of potentially clinically significant changes in these assessments was low throughout the study (Supplemental Table S2). Most changes in clinical

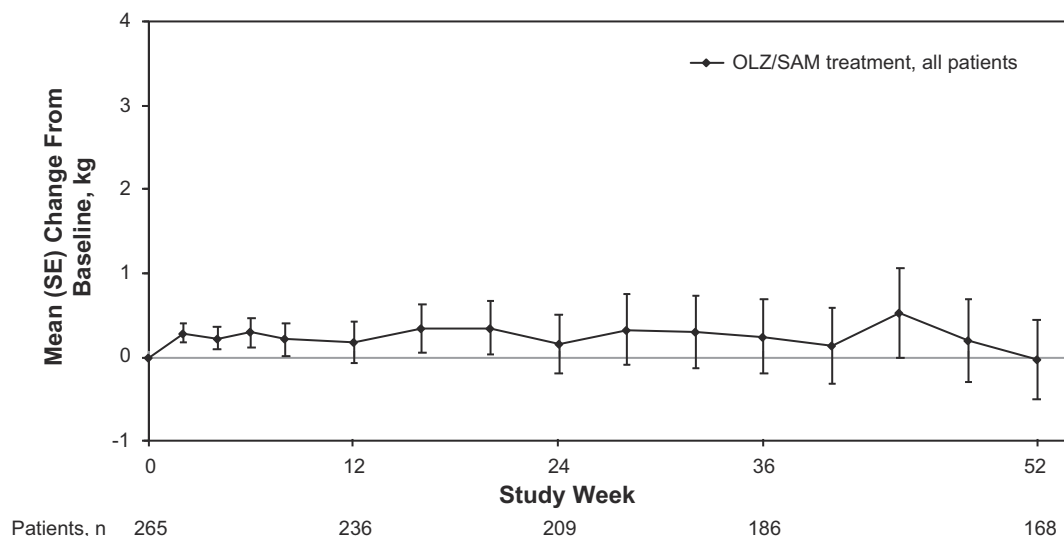


Fig. 3. Mean (SE) body weight changes from baseline to week 52. Baseline was relative to the first OLZ/SAM dose administered in this extension study (ENLIGHTEN-2-EXT). OLZ/SAM, combination of olanzapine and samidorphan.

assessments were transient; however, 2 of these instances resulted in treatment discontinuation for 2 patients (abnormal T wave on ECG, $n = 1$; gamma-glutamyl transferase increased, $n = 1$). No patients met the laboratory criteria for Hy's Law (ie, elevated alanine aminotransferase or aspartate aminotransferase at least 3 times the upper limit of normal [ULN], total bilirubin elevated at least 2 times the ULN, and alkaline phosphatase less than 2 times ULN) (Reuben, 2004) during the study.

The mean (SD) change in prolactin from baseline to week 52 was -5.5 (18.9) ng/mL in females ($n = 44$) and -0.9 (6.4) ng/mL in males ($n = 124$). Among patients with normal prolactin levels at baseline and at least 1 postbaseline assessment, 17/62 females (27.4%) and 24/177 males (13.6%) had prolactin levels that exceeded normal ranges (>30 ng/mL and >20 ng/mL, respectively) on at least 1 occasion during the study. An AE of increased prolactin occurred in 4 patients and led to treatment discontinuation in 1 female patient.

In general, rates of extrapyramidal symptoms were low. Mean (SD) changes in movement disorder assessments from baseline to week 52 ($n = 167$) were -0.1 (0.8) for the AIMS total, 0.0 (0.4) for the BARS global, and -0.1 (1.0) for the SAS total scores. Dyskinesia (defined as an AIMS score ≥ 3 on any of the first 7 items, or ≥ 2 on 2 or more of

the first 7 items) occurred in 6 (2.3%) patients. Parkinsonism (defined as an SAS total score > 3) and akathisia (defined as a BARS global score ≥ 2) occurred in 11 (4.2%) and 4 (1.5%) patients, respectively. Seven (2.6%) patients experienced AEs potentially related to extrapyramidal symptoms (4 with tremor, and 1 each with restlessness, muscle spasms, and muscle twitching) but none discontinued treatment due to an AE.

No suicides were reported. Based on C-SSRS scores, 18 (6.8%) patients experienced suicidal ideation. One patient (0.4%) who experienced suicidal ideation also had suicidal behavior per the C-SSRS (preparatory acts or behavior); this patient was considered to have a suicide-related AE that resolved and did not lead to study discontinuation.

3.6. Durability of treatment effect

In this 52-week study, the rate of all-cause discontinuation was 37% (98/265; Fig. 5), with 1 (0.4%) patient discontinuing because of lack of efficacy. Patients who enrolled in this extension were symptomatic but clinically stable at entry, with a baseline mean (SD) PANSS total score of 59.0 (11.8). PANSS total scores remained stable over the 52

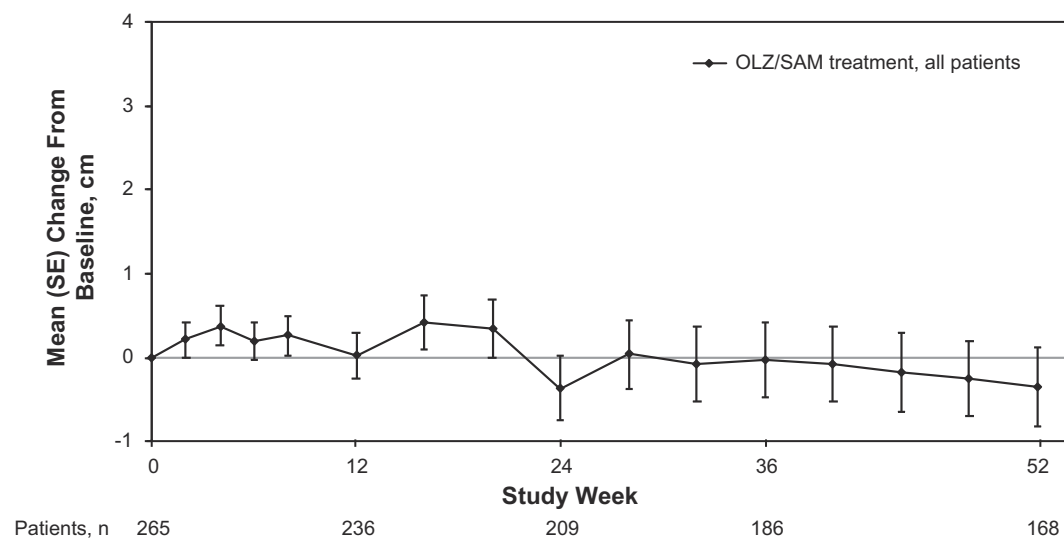


Fig. 4. Mean (SE) waist circumference changes from baseline to week 52. Baseline was relative to the first OLZ/SAM dose administered in this extension study (ENLIGHTEN-2-EXT). OLZ/SAM, combination of olanzapine and samidorphan.

Table 3Mean change from baseline to week 52 in fasting^a lipid and glycemic parameters, by visit.

Parameter	Baseline	4 weeks	12 weeks	24 weeks	36 weeks	52 weeks
Total cholesterol, fasting						
n	265	241	228	191	172	155
Mean (SD), mg/dL	186.9 (37.2)	187.9 (38.8)	184.3 (37.7)	184.5 (36.0)	181.6 (36.6)	181.5 (35.6)
Change from baseline, mean (SD), mg/dL	–	1.0 (23.4)	–1.9 (24.2)	–1.2 (26.2)	–2.1 (26.9)	–2.4 (26.5)
HDL cholesterol, fasting						
n	265	241	228	191	172	155
Mean (SD), mg/dL	57.0 (19.5)	56.6 (18.9)	55.9 (18.6)	56.7 (18.8)	55.9 (19.5)	56.3 (17.9)
Change from baseline, mean (SD), mg/dL	–	–0.4 (9.0)	–1.0 (10.8)	0.4 (11.5)	0.2 (11.4)	–1.3 (11.5)
LDL cholesterol, fasting						
n	265	241	228	191	172	155
Mean (SD), mg/dL	113.9 (33.7)	116.0 (36.7)	112.6 (35.1)	112.0 (32.3)	109.4 (34.3)	111.2 (34.6)
Change from baseline, mean (SD), mg/dL	–	1.3 (20.9)	–1.4 (22.1)	–1.9 (24.1)	–3.6 (26.5)	–1.5 (25.5)
Triglycerides, fasting						
n	265	241	228	191	172	155
Mean (SD), mg/dL	130.8 (88.8)	124.0 (81.5)	124.7 (77.8)	121.1 (72.5)	125.3 (115.3)	108.9 (61.5)
Change from baseline, mean (SD), mg/dL	–	–3.5 (72.8)	–3.6 (69.1)	–8.7 (68.5)	0.0 (117.2)	–10.7 (65.6)
Glucose, fasting						
n	265	241	228	189	173	154
Mean (SD), mg/dL	94.2 (14.1)	95.7 (15.2)	96.9 (16.5)	96.4 (16.0)	96.0 (16.8)	95.7 (16.0)
Change from baseline, mean (SD), mg/dL	–	2.0 (15.7)	2.5 (18.5)	2.7 (15.9)	1.0 (17.6)	1.3 (16.0)
HbA1c						
n	265	255	236	209	181	168
Mean (SD), %	5.5 (0.4)	5.5 (0.4)	5.5 (0.4)	5.5 (0.5)	5.5 (0.4)	5.5 (0.4)
Change from baseline, mean (SD), %	–	–0.01 (0.2)	0.02 (0.3)	0.04 (0.4)	0.02 (0.3)	0.03 (0.3)
Insulin, fasting						
n	265	238	221	193	168	153
Mean (SD), μU/mL	15.6 (24.7)	15.1 (13.9)	16.0 (17.4)	15.6 (18.3)	14.2 (15.2)	16.0 (28.3)
Change from baseline, mean (SD), μU/mL	–	–0.3 (27.2)	0.5 (28.2)	1.7 (18.9)	0.5 (16.6)	2.5 (29.0)

HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^a Fasting status was based on patient self-report without independent confirmation.

weeks of treatment (Fig. 6). For all patients completing treatment at week 52 ($n = 168$), the mean (SD) PANSS total score was 58.3 (12.1), and the mean change from baseline was -0.2 (8.5) (Supplemental Table S3).

Based on CGI-S scores at baseline, patients entered this study with mild to moderate disease severity on average (mean CGI-S score of 3.1). Consistent with PANSS total score findings, symptom control was maintained over 52 weeks of OLZ/SAM treatment as assessed by CGI-S; the mean CGI-S score for patients with an available assessment ($n = 166$) at week 52 was 3.0, corresponding to a mean change of -0.11 points

(Supplemental Table S3). Throughout the study, more than 74% of patients had CGI-S scores of 1 to 3 (normal to mildly ill; Fig. 7). In addition, for patients with available CGI-S scores at each visit, at least 90% who entered the study with a CGI-score of 3 or less maintained this level of mild disease severity over 52 weeks of OLZ/SAM treatment. Few patients experienced a worsening of disease severity (Supplemental Table S4).

4. Discussion

In this open-label study, OLZ/SAM was generally well tolerated in adults with schizophrenia who received treatment for up to 52 weeks. The tolerability of OLZ/SAM is supported by the overall study completion rate, the low rate of discontinuation attributable to AEs and the low incidence of SAEs. Long-term treatment with OLZ/SAM was associated with sustained antipsychotic efficacy and minimal effects on weight, waist circumference, and metabolic parameters over 52 weeks of treatment.

In the antecedent 24-week ENLIGHTEN-2 study, patients treated with OLZ/SAM and olanzapine gained weight. However, after an initial 4 to 6 weeks of treatment, weight stabilized with OLZ/SAM, whereas weight continued to increase with olanzapine throughout the remainder of the study (Correll et al., 2020). Here, treatment with OLZ/SAM for an additional 52 weeks resulted in a minimal weight change from study baseline. Furthermore, weight change profiles in this extension study were similar for those patients who had previously received OLZ/SAM and those who had received olanzapine over the 24-week ENLIGHTEN-2 study prior to enrollment in the extension, indicating that OLZ/SAM stabilized weight, even in patients with prior olanzapine-associated weight gain. Continued weight gain, which might be expected with ongoing olanzapine treatment, was not observed in those patients. The long-term stability of weight observed in this study contrasts with the weight profile reported historically in long-term trials of olanzapine in which weight gain continued over several months and even years, with considerable proportions of patients ($\approx 35\%$ – 64%) gaining at least 7% of their baseline body weight (Bushe et al., 2013; Kinon et al., 2001; Schoemaker et al., 2010; Zyprexa PI, 2020). The possibility of improved safety outcomes with OLZ/SAM, namely reduced weight gain relative to olanzapine (Correll et al., 2020)

Table 4Proportion of patients with anytime or sustained^a potentially clinically significant value shifts in fasting^b lipid and glycemic parameters from baseline to week 52.

Shift category	Anytime, all patients, n/m (%) ^c	Sustained, all patients, n/m (%) ^c
Glucose		
<126 to ≥ 126 mg/dL	29/254 (11.4)	1/229 (0.4)
HbA1c		
<5.7% to $\geq 5.7\%$	49/174 (28.2)	17/154 (11.0)
Total cholesterol		
<240 mg/dL to ≥ 240 mg/dL	24/238 (10.1)	1/217 (0.5)
HDL cholesterol		
≥ 40 mg/dL to <40 mg/dL	33/215 (15.3)	5/199 (2.5)
LDL cholesterol		
<160 mg/dL to ≥ 160 mg/dL	32/237 (13.5)	5/215 (2.3)
Triglycerides		
<200 mg/dL to ≥ 200 mg/dL	37/222 (16.7)	5/203 (2.5)

HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCS, potentially clinically significant.

^a Data are presented both for patients meeting PCS shift criteria at any postbaseline visit (anytime) and for patients meeting PCS criteria at their last two on-treatment assessments (sustained).^b Fasting status was based on patient self-report without independent confirmation.^c n is the number of patients who met the shift category; for PCS criterion based on the absolute value, m is the number of patients with a non-PCS baseline as well as ≥ 2 postbaseline assessments for the analysis of sustained PCS; for PCS criterion based on the change, m is the number of patients with a baseline value as well as ≥ 2 postbaseline assessments for the analysis of sustained PCS.

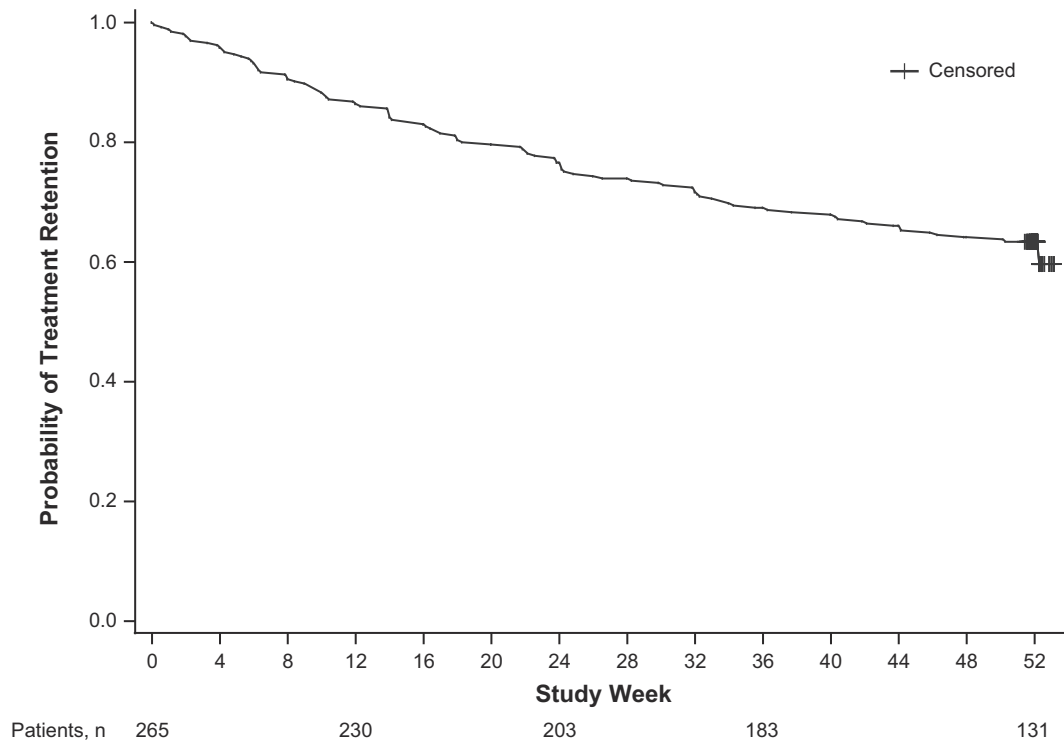


Fig. 5. Time to all-cause study discontinuation. Numbers at the bottom of the figure indicate the number of patients at risk at the corresponding study week. Patients who did not discontinue prematurely were censored at the time of their last dose of study drug (at approximately week 52, depending on the scheduling of the last dose). Because the number of patients who were censored in the final week of the study was large, individual censor symbols overlap.

and the stability of weight over 52 weeks of OLZ/SAM treatment observed in this study, indicate that OLZ/SAM may be a potential long-term treatment option for patients with schizophrenia or bipolar I disorder who could benefit from the known efficacy of olanzapine (Cipriani et al., 2011; Huhn et al., 2019; Leucht et al., 2009; Yildiz et al., 2015), but for whom the potential for weight gain might otherwise preclude its use.

During the 24-week ENLIGHTEN-2 study, separation in waist circumference favoring OLZ/SAM versus olanzapine was apparent beginning at week 1. This separation continued (ie, changes from baseline were smaller for OLZ/SAM) at all subsequent assessments (Correll et al., 2020). Additional changes in waist circumference during the 52-week extension study were minimal and suggest that the trajectory of

waist circumference increases associated with olanzapine treatment may be mitigated with OLZ/SAM. Waist circumference is a measure of central adiposity and is one criterion for diagnosis of metabolic syndrome, an important predictor of cardiovascular disease risk and diabetes. In addition, increases in waist circumference are associated with higher overall mortality (Alberti et al., 2009; Cerhan et al., 2014). An ongoing study of OLZ/SAM (NCT03187769) is assessing waist circumference and other outcomes (such as changes in body weight, safety, and CGI-S scores) associated with OLZ/SAM treatment. By mitigating increases in weight and waist circumference, OLZ/SAM has the potential to improve long-term health outcomes for patients with schizophrenia or bipolar I disorder. However, a full evaluation of

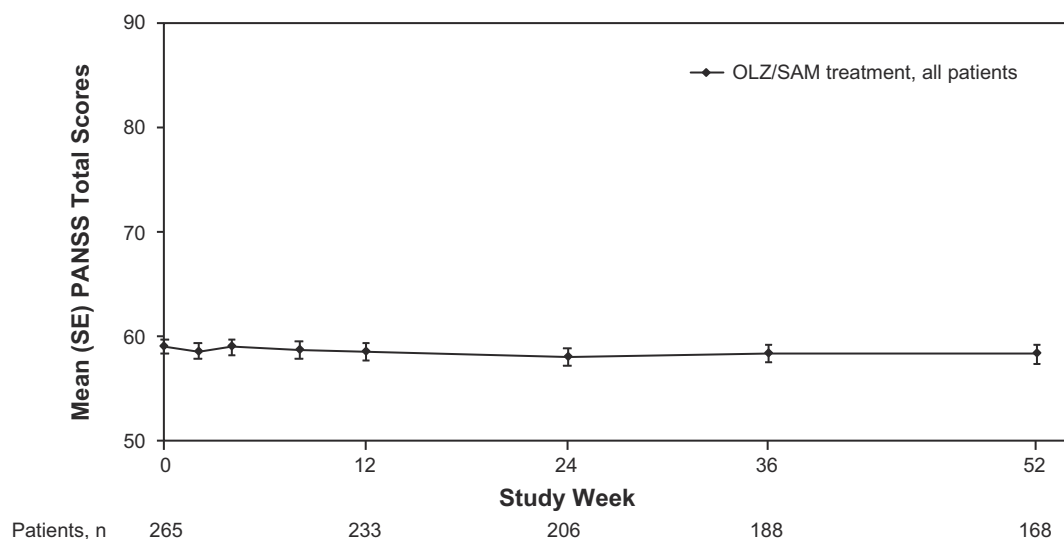


Fig. 6. Mean (SE) PANSS total score by visit from baseline to week 52. PANSS, Positive and Negative Syndrome Scale.

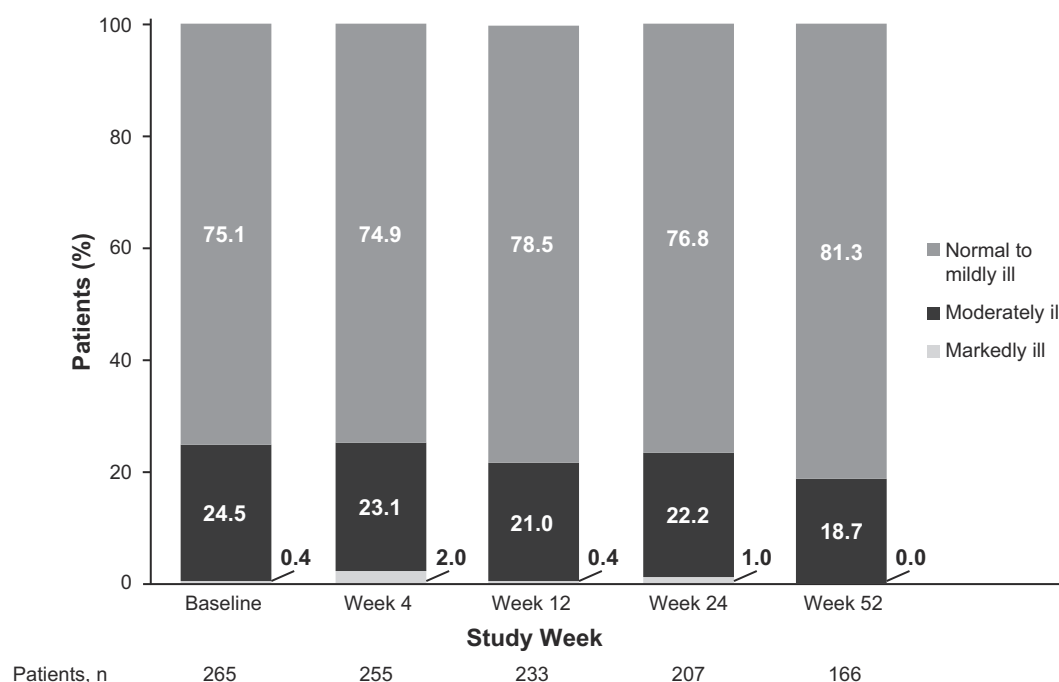


Fig. 7. CGI-S severity distribution from baseline to week 52. Normal to mildly ill, CGI-S score ≤ 3 ; moderately ill, CGI-S score = 4; markedly ill, CGI-S score ≥ 5 . CGI-S, Clinical Global Impression-Severity.

metabolic risk with OLZ/SAM will require real-world data from large populations, with long-term follow-up.

Overall, small net decreases from baseline were observed in fasting cholesterol and triglycerides over 52 weeks, and fewer than 4% of patients had sustained changes in any of these values that were of potential clinical significance. OLZ/SAM treatment over 52 weeks was associated with small changes from baseline in HbA1c and fasting insulin concentrations, consistent with results observed in the 52-week ENLIGHTEN-1-EXT (Yagoda et al., 2020). Together, these results suggest that glycemic control (WHO, 2011) is maintained with long-term OLZ/SAM treatment. In addition, most PCS values were transient, rather than sustained events, as indicated by the substantially higher proportion of patients meeting anytime PCS criteria versus those with sustained PCS metabolic laboratory values.

Symptom improvement observed during the 24-week phase 3 ENLIGHTEN-2 study (Correll et al., 2020) was maintained with long-term OLZ/SAM treatment in this 52 week extension, based on both PANSS total scores and CGI-S ratings. The relatively high retention rate for patients receiving long-term OLZ/SAM was consistent with the known efficacy profile of olanzapine, which has been characterized in previous reports by low rates of all-cause discontinuations in long-term trials (Haro et al., 2007; Kahn et al., 2008; Lieberman et al., 2005).

This study is limited by several factors. The loss of randomization upon entering the extension study and lack of a comparator in this open-label study limits the conclusions that may be drawn from safety and efficacy data. In addition, the 37% study discontinuation rate and missing data attributable to the long-term duration of this study may have impacted the results. However, the generalizability of these results is strengthened by the fact that the baseline demographics and clinical characteristics were similar among individuals who completed or discontinued the study. Furthermore, patients in this study were clinically stable at baseline, with an established response to olanzapine in ENLIGHTEN-2; thus, these findings may not be generalizable to patients experiencing acute schizophrenia exacerbations (although results from a previously reported study indicate antipsychotic efficacy of OLZ/SAM in this patient group; see Potkin et al., 2020). The study design of ENLIGHTEN-2, which preceded this extension, may have enriched for

patients who were relatively resistant to antipsychotic weight gain (length of disease history or body mass index of enrolled patients). Two ongoing phase 3 studies will provide additional data on the weight and metabolic effects of OLZ/SAM in patients with minimal prior antipsychotic exposure (NCT03187769) and in patients with up to 4 years of treatment (NCT03201757), respectively. Finally, fasting requirements can be challenging in this patient population and difficult to control in this type of study design. An important limitation of this study is that fasting status was self-reported by patients. As a result, it is possible that not all blood samples were obtained from patients in a fasted state.

5. Conclusions

OLZ/SAM was well tolerated over 52 weeks of treatment. Weight, waist circumference, and metabolic parameters were stable over 52 weeks of treatment. The long-term durability of OLZ/SAM treatment was evidenced by sustained improvements in symptoms of schizophrenia over 52 weeks, following 24 weeks of double-blind treatment with either OLZ/SAM or olanzapine. OLZ/SAM represents a potential new long-term treatment option for patients by providing the established efficacy and safety of olanzapine, with less weight gain.

Contributors

All authors had full access to the data, contributed to data interpretation, and participated in the drafting, critical review, and revision of the manuscript. All authors granted approval of the final manuscript for submission.

Role of the funding source

This study was sponsored by Alkermes, Inc. Alkermes employees were involved in the study design; the collection, analysis, and interpretation of data; the review of the manuscript; and the decision to submit for publication.

Declaration of competing interest

R. Kahn has served or currently serves as a consultant for Alkermes, Inc., Lundbeck, Merck, Otsuka, Roche, and Sunovion; has received speaker fees from Janssen-Cilag, Lundbeck, and Otsuka. B. Silverman, L. DiPetrillo, C. Graham, Y. Jiang, J. Yin, A. Simmons, V. Bhupathi, B. Yu, S. Yagoda, and C. Hopkinson are employees of Alkermes, Inc. or were employees at the time of this study. D. McDonnell is an employee of Alkermes Pharma Ireland Ltd.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2021.04.009>.

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