Olanzapine Plus Samidorphan (ALKS 3831) in Schizophrenia and Comorbid Alcohol Use Disorder: A Phase 2, Randomized Clinical Trial

Mary F. Brunette, MD[a,*]; Christoph U. Correll, MD[b,c]; Stephanie S. O'Malley, PhD[d]; David McDonnell, MD[e]; Lauren DiPetrillo, PhD[f]; Ying Jiang, PhD[f]; Adam Simmons, MPH[f]; Bernard L. Silverman, MD[f]; Leslie Citrome, MD, MPH[g]; and Alan I. Green, MD[a]

ABSTRACT

Objective: Alcohol use disorder (AUD) is a common comorbidity of schizophrenia. No effective pharmacologic treatment is available for both disorders to date.

Methods: In a phase 2, double-blind study, patients with schizophrenia and AUD experiencing ≥ 10 drinking and ≥ 2 heavy-drinking days in the previous month and recent (≤ 6 mo) disease symptom exacerbation were recruited between June 2014 and March 2017. *DSM-IV-TR* and *DSM-5* criteria were used to assign the diagnoses of schizophrenia and AUD, respectively. After a 6-week lead-in period, 234 eligible patients were randomized (1:1) to olanzapine + 10 mg samidorphan tablets (OLZ/SAM) or olanzapine + placebo tablets (olanzapine) for 36–60 weeks of treatment. The primary outcome of time to the first event of exacerbation of disease symptoms (EEDS) was evaluated using the log rank test for treatment comparison, and the Cox proportional-hazards model was used to estimate hazard ratio. Safety was assessed as adverse events and laboratory measures.

Results: No significant difference was observed between groups in the time to first EEDS (hazard ratio = 0.91; 95% CI, 0.53–1.56; $P = .746$). Patients treated with OLZ/SAM vs olanzapine had numerically lower rates in 6 of 8 criteria to evaluate EEDS. Change from baseline in percentage of heavy-drinking days during the double-blind treatment period was similar in OLZ/SAM- vs olanzapine-treated patients. OLZ/SAM was generally well tolerated with a safety profile similar to olanzapine.

Conclusions: OLZ/SAM was not superior to olanzapine in the time to EEDS and was well tolerated in patients with schizophrenia and AUD. Further research is needed to identify effective treatments for this difficult-to-treat population.

Trial Registrations: ClinicalTrials.gov identifier: NCT02161718; EudraCT number: 2014-001211-39

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[a]Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire
[b]Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, New York
[c]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany
[d]Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut
[e]Alkermes Pharma Ireland Limited, Dublin, Ireland
[f]Alkermes, Inc, Waltham, Massachusetts
[g]New York Medical College, Valhalla, New York
*Corresponding author: Mary F. Brunette, MD, Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756 (Mary.F.Brunette@hitchcock.org).

Alcohol use disorder (AUD) is a common comorbidity that occurs with schizophrenia and has a worldwide median lifetime prevalence of 20.6%.[1] In the United States, 1 in 3 people with schizophrenia have met the criteria for AUD,[2] and the odds of developing AUD in those with severe mental disorders is higher relative to the general population.[3] Comorbid AUD in patients with schizophrenia is associated with a heightened risk of nonadherence to medication,[4] high levels of inpatient treatment, and violent offending.[5]

Integrated psychosocial treatments, such as motivational and behavioral interventions that address both schizophrenia and AUD, are an important option in clinical practice.[6–9] Evidence of the long-term benefit of such interventions is, however, inconclusive,[10] and the risk of relapse is high.[11] Furthermore, few studies[12–14] have evaluated whether pharmacologic interventions can address alcohol misuse and associated symptom exacerbations in patients with schizophrenia and comorbid AUD. While no randomized controlled trial has reported reductions in alcohol use with antipsychotic treatment, some evidence supports better substance use disorder outcomes with clozapine over usual treatment[15] and long-acting injectable risperidone over daily oral risperidone[14] in this difficult-to-treat population[16]; however, no treatment is yet approved by the US Food and Drug Administration for this indication. Although olanzapine is considered one of the most efficacious first-line antipsychotics for schizophrenia,[17] patients with comorbid disorders have often been excluded from trials, and no prospective, controlled trials have evaluated olanzapine's impact in schizophrenia and comorbid AUD.

The literature supports targeting μ-opioid receptors in the management of people with substance use disorders.[18,19] In patients with schizophrenia and AUD, there is evidence (albeit limited) that supports the use of an opioid antagonist in reducing alcohol craving and drinking.[20] Samidorphan is a new chemical entity that is an opioid receptor antagonist.[21] In vivo, samidorphan has been demonstrated to function as a μ-opioid antagonist.[22] In vitro, samidorphan binds with high affinity to human μ-, κ-, and δ-opioid receptors and acts as an antagonist at μ-opioid receptors and partial agonist at κ- and δ-opioid receptors.[23] In a phase 2 study,[24] samidorphan reduced

Clinical Points

- Alcohol use disorder (AUD), although very common in patients with schizophrenia, is often not considered when clinicians are developing treatment plans that tend to focus on psychosis.
- Although no antipsychotics are indicated for treating AUD in patients with schizophrenia, there may be clinical benefits through reduced drinking in patients who are treated with antipsychotics such as olanzapine.
- In this randomized trial, olanzapine + 10 mg of samidorphan (an opioid receptor antagonist) was well tolerated but not superior to olanzapine over the 36- to 60-week treatment period regarding the primary outcome of time to first event of exacerbation of disease (AUD or schizophrenia) symptoms.

the cumulative proportion of heavy-drinking days in patients with AUD.

ALKS 3831, a combination of flexible-dose olanzapine and 10 mg of samidorphan (OLZ/SAM), is under investigation for the treatment of schizophrenia.[25] In a phase 2 study[26] in patients with schizophrenia, OLZ/SAM had similar efficacy to olanzapine alone, with significant mitigation of weight gain, and was well tolerated. Because samidorphan alone reduced alcohol drinking in patients with AUD,[24] we conducted a study to evaluate the efficacy, safety, and tolerability of OLZ/SAM, administered as 2 tablets, compared with olanzapine and matched placebo tablets (olanzapine) in a phase 2, randomized, double-blind study in patients with schizophrenia and comorbid AUD.

METHODS

This phase 2, double-blind, placebo-controlled study in patients with schizophrenia and AUD took place across multiple sites in the United States, Bulgaria, and Poland between June 2014 and March 2017 (ClinicalTrials.gov identifier: NCT02161718; EudraCT Number: 2014-001211-39). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles outlined in the International Conference on Harmonization. The protocol and informed consent form were approved by an Institutional Review Board/Independent Ethics Committee at each study site prior to recruitment, and written informed consent was obtained for all participants.

Full details of the study design and assessments have been reported elsewhere.[27] Briefly, outpatients with schizophrenia, AUD, and a recent acute exacerbation (within 6 months) participated in a 6-week lead-in phase involving open-label olanzapine once daily for 4 weeks (dose determined by the investigator) to ensure that the subjects were able to tolerate olanzapine. Subsequently, patients were treated for 2 weeks with both open-label olanzapine (fixed dose) and samidorphan tablets, taken simultaneously. After the 6-week lead-in phase, eligible patients were randomized (1:1) to daily OLZ/SAM or olanzapine for a double-blind treatment phase lasting a minimum of 36 weeks and a maximum of 60 weeks, with an additional 3-week safety follow-up with open-label olanzapine.

During the double-blind treatment period, patients attended an outpatient visit every 2 weeks for drug dispensing. Clinical and safety assessments were conducted every 4 weeks.

Patients

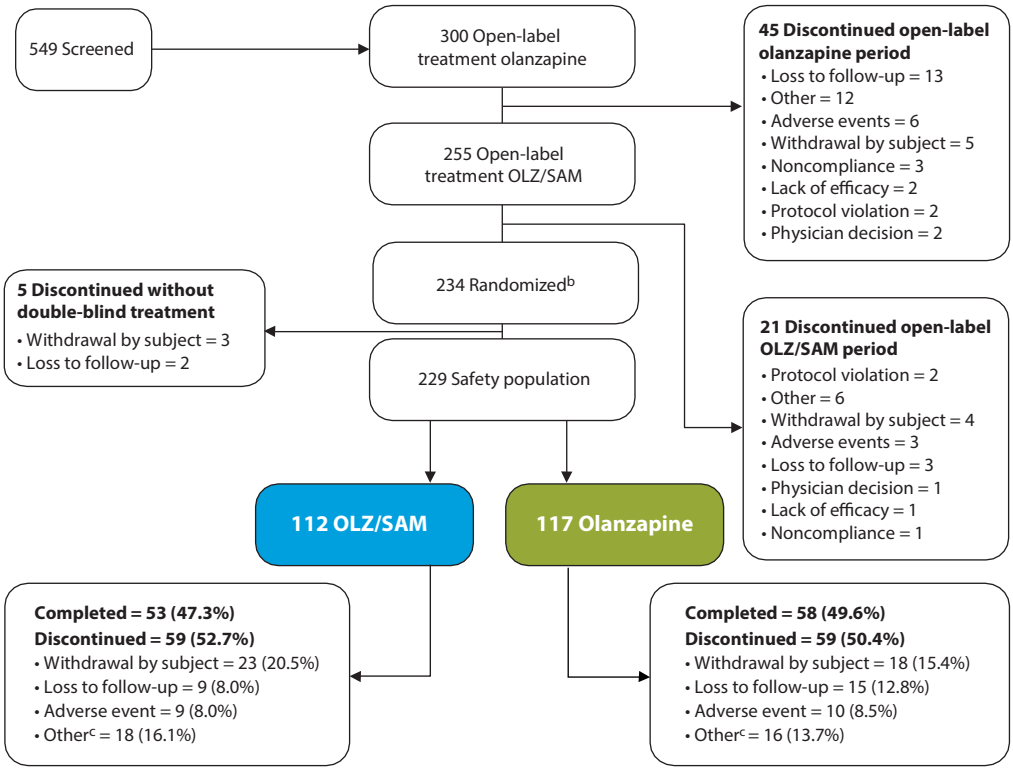
Men and women aged 18–65 years with a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision[28] (*DSM-IV-TR*) criteria who met prespecified symptom severity criteria and a diagnosis of AUD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition[29] (*DSM-5*) and who had 10 or more drinking and 2 or more heavy-drinking days in the past month with recent (≤ 6 mo) disease symptom exacerbation were recruited. No abstinence was required. Key exclusion criteria included intolerance to olanzapine and a positive test for opioids. Those who had, in the past year, a *DSM-5* diagnosis of other substance use disorders were excluded because other substance use disorders were not expected to respond to OLZ/SAM and could impact the primary outcome.[27] Benzodiazepines (except prior to visit 8 when medically indicated) and all alcohol treatment–related medications, including, but not limited to, naltrexone, naloxone, acamprosate, and disulfiram, were prohibited during the study.

Supportive counseling was provided as per investigator's judgment at specified monthly visits. Counseling focused on the following: (1) disease education, (2) encouragement of treatment adherence, and (3) crisis intervention. The person who conducted supportive counseling sessions was recommended not to assist the subject with timeline follow-back (TLFB). Compliance with study medication was monitored through pill counts at medication dispensing visits every 2 weeks.

Study Outcomes

The primary endpoint was the time to the first event of exacerbation of disease symptoms (EEDS) based on any of 8 prespecified events that were related to worsening of AUD or schizophrenia, confirmed by a blinded, independent adjudication committee. EEDS included (1) hospitalization due to worsening psychiatric symptoms, alcohol intoxication, or alcohol withdrawal (investigators attempted to obtain records to confirm self-report of EEDS); (2) worsening in Positive and Negative Syndrome Scale[30] (PANSS) total score (determined by a ≥ 25% or ≥ 15-point increase from randomization), as confirmed at a second visit shortly after the first assessment; (3) confirmed worsening in PANSS item score (P1, P2, P3, P6, P7, or G8; delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, or uncooperativeness, respectively) from baseline; (4) deliberate self-injury, aggressive behavior, or showing signs of clinically significant suicidal or homicidal

Figure 1. Patient Disposition[a]



[a]Percentage values in parentheses are relative to the safety population.
[b]Five patients were randomized but did not receive study drug: loss to follow-up, n = 2 (OLZ/SAM); withdrawal by patient, n = 3 (2 OLZ/SAM, 1 olanzapine).
[c]For OLZ/SAM and olanzapine, respectively, includes other (n = 6; n = 6), noncompliance with study drug (n = 8; n = 2), physician decision (n = 2; n = 4), protocol violation (n = 2; n = 3), and lack of efficacy (n = 0; n = 1).
Abbreviations: OLZ/SAM = olanzapine/samidorphan 10 mg.

ideation; (5) administration of rescue medication or increased olanzapine dose due to worsening symptoms; (6) an emergency-room visit; (7) discontinuation for lack of efficacy, loss to follow-up, or withdrawal by the patient; and (8) arrest or incarceration. Patients were allowed to continue the study after an occurrence of an EEDS.

Secondary endpoints were the rate and number of EEDS and the proportion of patients with a ≥ 1 level decrease in World Health Organization (WHO) drinking risk level from baseline to week 24 of the double-blind treatment period. Alcohol use was calculated using the following equation[31,32]: alcohol consumption per day = total number of standard drinks × 14 g/total number of days. Subsequently, WHO drinking risk level was determined according to alcohol consumption (g) per drinking day: abstinence (0 g); low risk (men 1–40 g, women 1–20 g); medium risk (men 41–60 g, women 21–40 g); high risk (men 61–100 g, women 41–60 g); and very high risk (men ≥ 101 g, women ≥ 61 g).[31,32]

Other outcomes included the number of heavy-drinking days (HDDs)—defined as ≥ 4 drinks in a day for women and ≥ 5 drinks in a day for men[31]—that was assessed using the TLFB method[33] for the period between study visits, and the desire for alcohol, which was assessed by the change from baseline in visual analog scale (VAS) score over the duration of the study. Schizophrenia symptoms, based on the change from baseline in PANSS total scores and the Clinical Global Impressions–Severity of Illness scale[34] (CGI-S) global score, were also evaluated. Safety was assessed by adverse events (AEs), Columbia–Suicide Severity Rating Scale[35] (C-SSRS), vital signs, electrocardiogram, and laboratory assessments. An analysis of the time from randomization to first EEDS by percent of HDDs during the double-blind treatment period was also conducted to explore the relationship of EEDS to the drinking profile.

Statistics

Statistical analysis was performed on the intention-to-treat (ITT) population (same as the safety population), defined as all randomized patients who received at least 1 dose of OLZ/SAM or olanzapine during the double-blind treatment period. The primary endpoint, time to first EEDS, was evaluated using the log rank test for treatment comparison, and the Cox proportional-hazards model was used to estimate the hazard ratio, adjusting for relevant covariates. Kaplan-Meier estimates of EEDS rate were generated. Time to recurrent EEDS was analyzed by an Andersen-Gill mean/rate intensity model.

Table 1. Baseline Characteristics of Safety Population at Randomization[a]

Characteristic	OLZ/SAM (n = 112)	Olanzapine (n = 117)
Age, y	46.4 (10.6)	45.1 (10.2)
Male, n (%)	89 (79.5)	91 (77.8)
Black, n (%)	65 (58.0)	57 (48.7)
Current smoker, n (%)	92 (82.1)	93 (79.5)
BMI, kg/m^2	28.6 (5.7)	28.5 (5.4)
Olanzapine dose, mg/d	14.00 (6.6)	14.98 (6.8)
Schizophrenia severity		
PANSS total score	64.9 (7.9)	64.4 (7.7)
PANSS positive score	15.8 (2.9)	15.2 (3.9)
PANSS negative score	17.8 (4.0)	17.8 (4.)
PANSS general score	31.3 (4.9)	31.5 (4.4)
CGI-S scale score	3.4 (0.7)	3.5 (0.6)
Past 12-mo psychiatric hospitalizations	0.6 (0.9)	0.8 (1.3)
Alcohol use severity		
No. of drinks/d	3.7 (3.5)	3.0 (2.2)
No. of drinks/drinking day	5.3 (3.9)	4.7 (2.8)
No. of AUD-related hospitalizations in previous 12 mo	0.1 (0.5)	0.2 (0.5)
Severe AUD,[b] n (%)	98 (87.5)	88 (75.2)
% HDDs[c]	33.6 (33.0)	27.0 (26.8)
WHO drinking risk,[d] n (%)		
Abstinence	3 (2.7)	6 (5.1)
Low risk	46 (41.1)	50 (42.7)
Medium risk	35 (31.3)	28 (23.9)
High risk	13 (11.6)	24 (20.5)
Very high risk	15 (13.4)	9 (7.7)

[a]All values are mean (SD) unless otherwise noted.
[b]Severe AUD, assessed at screening, was defined as the presence of 6 or more symptoms (of 11) at screening as per *DSM-5* criteria.
[c]HDDs, based on the 2-week period prior to randomization, were defined as ≥ 5 drinks in 1 day for men and ≥ 4 drinks in 1 day for women.
[d]At each visit, alcohol consumption was calculated based on the number of drinks per day as follows: alcohol consumption per day = total number of drinks × 14 g/total number of days. WHO drinking risk levels were defined according to alcohol consumption (g) per drinking day, based on the 2-week period prior to randomization: abstinence (0 g); low risk (men 1–40 g, women 1–20 g); medium risk (men 41–60 g, women 21–40 g); high risk (men 61–100 g, women 41–60 g); very high risk (men ≥ 101 g, women ≥ 61 g).[31,32]
Abbreviations: AUD = alcohol use disorder; BMI = body mass index; CGI-S = Clinical Global Impressions–Severity of Illness; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; HDD = heavy-drinking day; OLZ/SAM = olanzapine/samidorphan 10 mg; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; WHO = World Health Organization.

Changes in PANSS total scores and CGI-S scale global score from baseline until the end of the double-blind treatment phase (36–60 weeks) were calculated using an analysis of covariance (ANCOVA) approach with last observation carried forward (LOCF) imputation for missing data in the ITT population. Additionally, post hoc analyses of the change in PANSS total scores and CGI-S global score were conducted by mixed model with repeated measurements (MMRM) and presented as least squares (LS) mean and standard error (SE). Cohen *d*[36] was used to assess overall treatment effect sizes for PANSS total score and CGI-S global score. According to Cohen, 0.2 is considered a small effect size and 0.5 is a medium effect size.[36,37] The proportion of patients with change in WHO drinking risk level at week 24 of the double-blind treatment period (secondary endpoint) and absence of HDDs over the study period were analyzed by logistic regression. Descriptive statistics were used to assess the change in percentage of HDDs. Change in VAS for perception of desire for alcohol was analyzed using ANCOVA based on LOCF. Descriptive summary statistics were used for all safety measures.

It was estimated that a sample size of approximately 70 events out of 270 randomized patients (135 patients per treatment group) would provide approximately 90% power to detect a hazard ratio of 0.45 between OLZ/SAM and olanzapine in time to first EEDS.

RESULTS

Patients and Treatment

Disposition is reported in Figure 1. Overall, 549 patients were screened, 300 were enrolled into olanzapine open-label treatment of which 255 continued OLZ/SAM open-label treatment, and 234 were randomized into the double-blind treatment period (olanzapine). Fewer patients were randomized than the target of 270 due to challenges with enrolling patients with schizophrenia and comorbid AUD. Five patients randomized did not receive study drug due to loss to follow-up (n = 2; OLZ/SAM) and withdrawal by patient (n = 3; 2 OLZ/SAM, 1 olanzapine). In total, 53 (47.3%) patients receiving OLZ/SAM completed the study compared with 58 (49.6%) receiving olanzapine. Baseline demographics, alcohol use, and disease symptom characteristics were similar between treatment groups (Table 1). The mean daily (± standard deviation [SD]) dose of olanzapine prescribed after randomization was 14.0 ± 6.6 mg in the OLZ/SAM group and 15.0 ± 6.8 mg in the olanzapine group. Baseline rate of heavy-drinking days was higher in the OLZ/SAM group (both at screening and randomization); however, relative changes from baseline in reduction in HDDs was similar between groups. In addition, concomitant medication use was similar between groups.

Efficacy

There was no significant difference between the 2 treatment groups in the time to first EEDS (primary endpoint; hazard ratio [HR] = 0.91; 95% CI, 0.53–1.56; *P* = .746; Figure 2A). No significant difference was observed in the secondary endpoint, time to recurrent EEDS (HR = 0.77; 95% CI, 0.43–1.37; *P* = .372). The frequencies of the 8 criteria to evaluate EEDS are shown in Figure 2B.

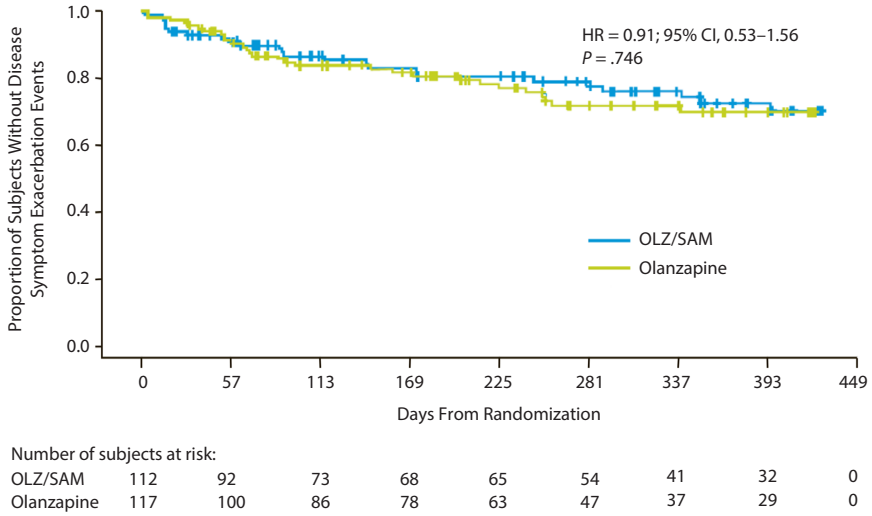
In an exploratory analysis of the time from randomization to first EEDS by percent of HDDs during the double-blind treatment period, heavy drinking was associated with earlier time to EEDS events compared with mild drinking (HR = 2.53, 95% CI, 1.23–5.23; *P* = .012; Supplementary Figure 1).

Alcohol Use

WHO drinking risk level. No between-group differences in alcohol use behavior were observed as measured by changes in WHO drinking risk level. At week 24, no difference in the proportion of subjects with a ≥ 1 level decrease (signifying improvement) in WHO drinking risk (secondary endpoint) was observed with the OLZ/SAM vs

Figure 2. Events of Exacerbation of Disease Symptoms

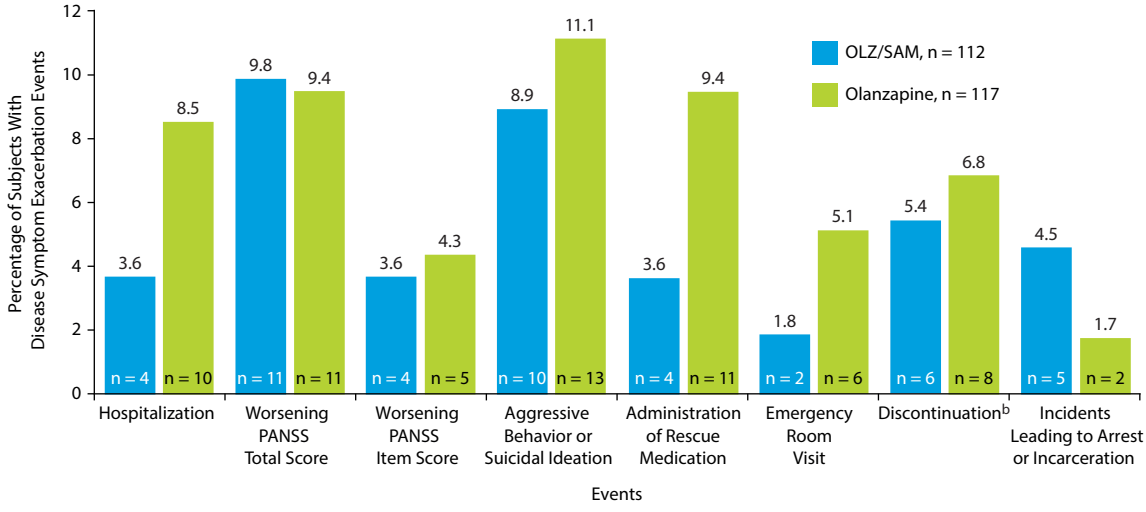
A. Time to First Event of Exacerbation of Disease Symptoms (ITT population)



Number of subjects at risk:

OLZ/SAM	112	92	73	68	65	54	41	32	0
Olanzapine	117	100	86	78	63	47	37	29	0

B. Total Events of Exacerbation of Disease Symptoms by Individual Component (ITT population)[a]



[a]No statistically significant differences were observed between treatment groups. The vertical tic marks on each line in the graph indicate when a patient was censored (subject discontinued without developing the event of analysis).
[b]Discontinuation for lack of efficacy, loss to follow-up, or withdrawal by patient.
Abbreviations: CI = confidence interval, HR = hazard ratio, ITT = intention-to-treat, OLZ/SAM = olanzapine/samidorphan 10 mg, PANSS = Positive and Negative Syndrome Scale.

olanzapine treatment groups (40.5% vs 37.9%, respectively; odds ratio [OR] = 0.99; 95% CI, 0.56–1.73]; $P = .963$). Shifts from baseline in WHO drinking risk categories are presented in Supplementary Table 1.

Heavy-drinking days. The change from baseline in the percentage of HDDs during the double-blind treatment period was similar in OLZ/SAM- vs olanzapine-treated patients: percentage (mean ± SD) of HDDs at week 36 were −21.2% ± 26.6% (n = 61) vs −15.0% ± 28.3% (n = 66), respectively, and at week 60 were −16.9% ± 22.9% (n = 31) vs −13.2% ± 31.5% (n = 32), respectively. From randomization through week 24 of the double-blind treatment period, absence of any HDDs was reported in 10.8% and 13.8% of OLZ/SAM- and olanzapine-treated patients, respectively (OR = 0.82; 95% CI, 0.36–1.90; $P = .649$).

Desire for alcohol. At baseline, the mean ± SD VAS rating of desire for alcohol was 51.7 ± 25.8 and 47.1 ± 22.8 for patients treated with OLZ/SAM and olanzapine, respectively. During the double-blind treatment period, a reduction in desire (LS mean ± SE decrease) for alcohol was observed with OLZ/SAM and olanzapine with no between-group differences at week 36 (−11.0 ± 2.4 [n = 102] vs −9.3 ± 2.3 [n = 113], respectively; LS mean difference ± SE: −1.6 ± 3.3; $P = .618$) and at week 60 (−12.0 ± 2.4 [n = 102] vs −9.4 ± 2.3 [n = 113], respectively; LS mean difference ± SE: −2.6 ± 3.4; $P = .441$).

Table 2. Safety Outcomes

Outcome	OLZ/SAM (n = 112) n (%)	Olanzapine (n = 117) n (%)
Any treatment-emergent AE	64 (57.1)	69 (59.0)
Treatment-related AE	36 (32.1)	32 (27.4)
AE severity		
Mild	31 (27.7)	35 (29.9)
Moderate	27 (24.1)	27 (23.1)
Severe	6 (5.4)	7 (6.0)
AE leading to treatment discontinuation	10 (8.9)	13 (11.1)
Serious AE	7 (6.3)[a]	12 (10.3)[b]
Death	1 (0.9)[c]	1 (0.9)[d]
AEs occurring in ≥ 3% of patients in any group		
Increased weight	16 (14.3)	14 (12.0)
Nasopharyngitis	7 (6.3)	5 (4.3)
ALT increased	6 (5.4)	0
Schizophrenia	5 (4.5)	6 (5.1)
Insomnia	4 (3.6)	3 (2.6)
Increased blood insulin	4 (3.6)	1 (0.9)
Toothache	4 (3.6)	1 (0.9)
AST increased	4 (3.6)	0
Hypertension	3 (2.7)	4 (3.4)
Headache	2 (1.8)	4 (3.4)
Suicidal ideation	0	4 (3.4)

[a]Serious AEs reported with OLZ/SAM (8 events reported in 7 patients): schizophrenia worsening, n = 5 (schizophrenia [n = 3], paranoia [n = 1], psychotic disorder [n = 1]); COPD complications, n = 1; ECG abnormality, n = 1; transient ischemic attack, n = 1.
[b]Serious AEs reported with olanzapine (13 events reported in 12 patients): schizophrenia worsening, n = 4; suicidal ideation, n = 3; behavioral disturbance, n = 2; aggressive behavior, n = 1; agitation, n = 1; alcohol poisoning, n = 1; parotitis, n = 1.
[c]Exacerbation of COPD.
[d]Alcohol poisoning.
Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, COPD = chronic obstructive pulmonary disease, ECG = electrocardiogram, OLZ/SAM = olanzapine/samidorphan 10 mg.

Schizophrenia Symptoms

PANSS total scores. Using an ANCOVA with LOCF, there was an overall improvement in LS mean of PANSS total scores in both treatment groups, as indicated by a decrease from randomization to week 63 of −5.4 (SE = 1.01) and −3.4 (SE = 0.99) in the OLZ/SAM and olanzapine groups, respectively ($P = .175$). A post hoc analysis, using an MMRM approach, of patients in the OLZ/SAM group had significantly greater improvements from baseline in PANSS total score vs patients treated with olanzapine. The LS mean ± SE decrease for OLZ/SAM (n = 61) vs olanzapine (n = 67) from baseline to week 36 was −6.9 ± 1.3 vs −3.3 ± 1.2, respectively (LS mean difference: −3.6 ± 1.8; $P = .043$). The overall treatment effect size for PANSS total score with OLZ/SAM compared with olanzapine at week 36 was 0.27 based on Cohen *d*. The LS mean ± SE decrease for OLZ/SAM (n = 30) vs olanzapine (n = 32) from baseline to week 60 was −8.9 ± 1.5 vs −3.6 ± 1.5 (LS mean difference: −5.3 ± 2.2; $P = .016$). The overall treatment effect size for PANSS total score with OLZ/SAM compared with olanzapine at week 60 was 0.32 based on Cohen *d*.

CGI-S scores. The LS mean ± SE decrease for OLZ/SAM (n = 61) vs olanzapine (n = 67) from baseline to week 36 in a post hoc analysis was −0.52 ± 0.08 vs −0.24 ± 0.08 (LS mean difference: −0.29 ± 0.11; $P = .013$). The overall treatment effect size for CGI-S scores with OLZ/SAM compared with olanzapine at week 36 was 0.34 based on Cohen *d*. The LS mean ± SE decrease for OLZ/SAM (n = 31) vs olanzapine (n = 32) from baseline to week 60 was −0.68 ± 0.11 vs −0.39 ± 0.11 (LS mean difference: −0.29 ± 0.15; $P = .065$). The overall treatment effect size for CGI-S scores with OLZ/SAM compared with olanzapine at week 60 was 0.25 based on Cohen *d*.

Safety

AEs were reported in 57.1% vs 59.0% of patients treated with OLZ/SAM vs olanzapine, respectively (Table 2). Alanine aminotransferase increase was the only AE with incidence of ≥ 5% in the OLZ/SAM group and at least twice the rate of olanzapine. The most commonly reported AEs (occurring in ≥ 3% of patients in both groups) were weight gain, nasopharyngitis, and exacerbation of schizophrenia symptoms. Most AEs were mild or moderate in severity and rates of AEs leading to discontinuation were similar between treatment groups. Eight serious AEs were reported in 7 patients receiving OLZ/SAM, all deemed unrelated to study treatment. A total of 13 serious AEs were reported in 12 patients receiving olanzapine. In 1 of these patients, a serious AE (agitation) was considered to possibly be related to study treatment but did not result in study discontinuation. One death occurred in each group: an exacerbation of chronic obstructive pulmonary disease in a patient receiving OLZ/SAM and alcohol poisoning in a patient receiving olanzapine; neither death was considered related to study treatment.

DISCUSSION

In this study, time to first EEDS among patients with schizophrenia and comorbid AUD was not significantly different between the groups treated with OLZ/SAM and olanzapine. As expected, heavier drinkers had higher rates of EEDS events. However, in both treatment groups, there was a reduction in alcohol use and improvement in psychiatric symptoms.

This study used a novel, population-specific primary endpoint (EEDS) that was specifically designed to combine prospectively defined indicators of either psychosis or substance use disorder symptom recurrences for a meaningful assessment of treatment outcomes.[27] Drinking among individuals with comorbid AUD may exacerbate the vulnerabilities associated with a diagnosis of schizophrenia,[38] resulting in increased symptoms and poor outcomes.[5] The reverse may also be true, and thus, exacerbations in psychosis symptoms may lead to increased drinking. This reciprocal relationship has been reported in patients with schizophrenia and cannabis use disorder.[39] In addition to EEDS, standard measures of symptoms (PANSS and CGI-S) and drinking (TLFB) were used.

The low rate of EEDS may have reduced the power to detect a difference between treatment groups. In addition, patients who met inclusion criteria for drinking at screening

may not have met these same criteria at baseline, as heavy drinking had decreased during that period. Potential causes of the low rate of EEDS include symptom and drinking improvement due to olanzapine treatment[40] and stabilization due to nonspecific effects of study participation. Although the OLZ/SAM group experienced greater improvements in PANSS total score and CGI-S global score from randomization to the end of the double-blind treatment phase (weeks 36–60) than the olanzapine group, this difference was not great enough to impact EEDS, and this post hoc finding requires replication with additional research.

Previous research[20,24,41] reported a positive effect on reducing drinking behavior of opioid antagonists in comorbid AUD patients that was not found with OLZ/SAM in this study, possibly due to differences in study populations or study design. For example, compared with those in the present study, patients in the study by Petrakis et al[20] at baseline had a lower degree of psychosis symptoms and heavier drinking levels. In addition, patients remained on their clinically chosen antipsychotic.[20] Furthermore, recent data[42] have proposed that treatment with a μ-opioid receptor antagonist may be more effective in individuals whose drinking is driven by reward and positive reinforcement. It is possible that reward drinkers were underrepresented in the population evaluated in this study.

Several study limitations warrant discussion. The lead-in period may have excluded the highest risk of relapse patients and also biased the patients to those that responded to olanzapine. In addition, the variable length of exposure to treatment after week 36 limits the interpretation of findings during the 36- to 60-week period. Possible floor effects due to AUD of insufficient severity and low rate of EEDS during follow-up may limit the ability to detect a differential impact of samidorphan. Excluding people with co-occurring other drug use disorders resulted in a sample that may not generalize to people with schizophrenia and AUD who also have other substance use disorders. The significant differences in PANSS total scores with the MMRM approach should be interpreted with caution as this was a post hoc analysis. Despite the limitations, this study highlights the feasibility of enrolling participants with schizophrenia and comorbid AUD in long-term treatment studies[12,13] and documents the general safety of OLZ/SAM in this higher risk population. To our knowledge, this study is the largest and longest conducted in this population to date.[27]

In summary, treatment with OLZ/SAM was not superior to olanzapine in the time to first EEDS and was well tolerated in the treatment of patients with schizophrenia and comorbid AUD. This study is of particular relevance as few clinical trials have been completed in patients with schizophrenia and comorbid AUD, and this trial demonstrates the feasibility of recruiting and conducting long-term evaluation of this difficult-to-treat patient population. Further research is needed to identify effective treatments for this group of patients who have been underrepresented in clinical research to date.

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Previous presentation: Brunette MA, et al. A phase 2, randomized, double-blind study of ALKS 3831 in schizophrenia and co-occurring alcohol use disorder presented their poster (#M212) at the 56th Annual Meeting of the American College of Neuropsychopharmacology (ACNP); December 3–7, 2017; Palm Springs, California. • O'Malley S, et al. Schizophrenia complicated by comorbid alcohol use disorder: symptom outcomes from a phase 2 randomized controlled trial presented their poster (#P6-149) at the American Psychiatric Association (APA) Annual Meeting; May 5–9, 2018; New York City, New York.

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Supplementary Material

Article Title: Olanzapine Plus Samidorphan (ALKS 3831) in Schizophrenia and Comorbid Alcohol Use Disorder: A Phase 2, Randomized Clinical Trial

Author(s): Mary F. Brunette, MD; Christoph U. Correll, MD; Stephanie S. O'Malley, PhD; David McDonnell, MD; Lauren DiPetrillo, PhD; Ying Jiang, PhD; Adam Simmons, MPH; Bernard L. Silverman, MD; Leslie Citrome, MD, MPH; and Alan I. Green, MD

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List of Supplementary Material for the article

1. Table 1 — Change from baseline in WHO drinking risk at Week 24 of the double-blind treatment period (ITT population)
2. Figure 1 — Kaplan-Meier plot of time to first EEDS by percent of HDDs during the double-blind treatment period (ITT population)

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Supplementary Table 1. Change from baseline in WHO drinking risk[a] at Week 24 of the double-blind treatment period (ITT population)

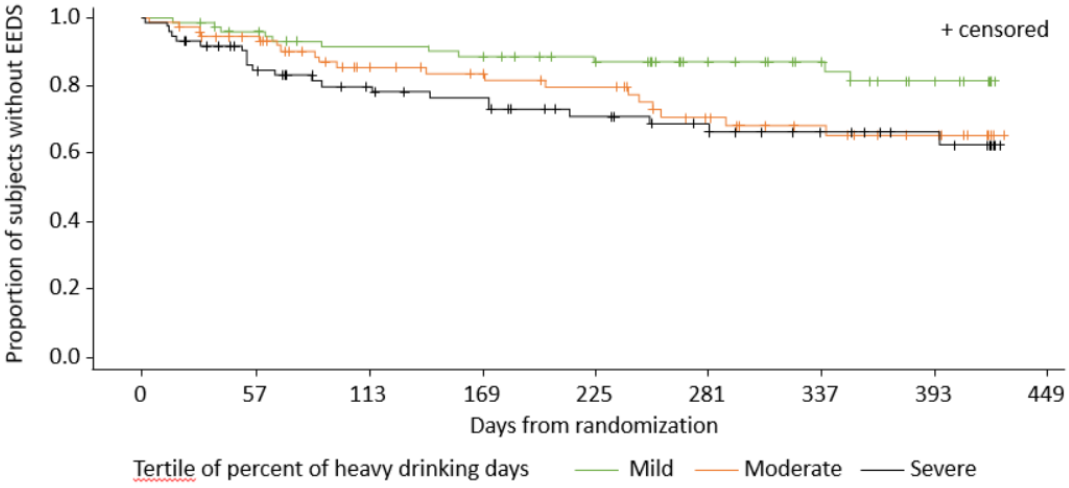
Baseline WHO drinking risk category	Improvement from baseline	OLZ/SAM[b] n/N (%)	Olanzapine[b] n/N (%)
Abstinence	N/A	3/3 (100.0)	6/6 (100.0)
Low risk	≥1 level	7/46 (15.2)	5/49 (10.2)
Medium risk	≥1 level	24/34 (70.6)	18/28 (64.3)
	≥2 level[c]	7/34 (20.6)	2/28 (7.1)
High risk	≥1 level	8/13 (61.5)	15/24 (62.5)
	≥2 level[c]	2/13 (15.4)	8/24 (33.3)
Very high risk	≥1 level	6/15 (40.0)	6/9 (66.7)
	≥2 level[c]	2/15 (13.3)	4/9 (44.4)

n, number of patients meeting criteria; N, number of patients with assessment

[a]At each visit, alcohol consumption per day was calculated based on the number of drinks per day as follows: alcohol consumption per day = total number of drinks × 14 grams (g)/total number of days. WHO drinking risk levels were defined according to alcohol consumption (g) per drinking day: abstinence (0 g); low risk (males 1–40 g, females 1–20 g); medium risk (males 41–60 g, females 21–40 g); high risk (males 61–100 g, females 41–60 g); very high risk (males ≥101 g, females ≥61 g)[31, 32]
[b]One patient receiving olanzapine (low risk at baseline) and one patient receiving OLZ/SAM (medium risk at baseline) did not have post-baseline TLFB measurement available
[c]The n numbers for a ≥2 level improvement are also included in the n numbers for ≥1 level improvement

ITT, intention to treat; N/A, not applicable; OLZ, olanzapine; PBO, placebo; SAM, samidorphan 10 mg; TLFB, timeline follow-back; WHO, World Health Organization

Supplementary Figure 1. Kaplan–Meier plot of time to first EEDS by percent of HDDs during the double-blind treatment period (ITT population)[a]



Number of subjects at risk

Mild	76	69	62	58	52	42	33	25	0
Moderate	76	65	49	44	40	30	24	19	0
Severe	75	58	48	44	36	29	21	17	0

[a]Heavy drinking (severe) was associated with earlier time to EEDS events compared to mild drinking (HR: 2.53; 95% CI: 1.23, 5.23; *P*=.012)

"+" indicates when the subject is censored (subject discontinued without developing the event of analysis); CI, confidence interval; ITT, intention to treat; EEDS, exacerbation of disease symptoms; HDD, heavy drinking day; HR, hazard ratio