Trial in Progress: A Randomized Double-Blind Trial Comparing OLZ/SAM vs Olanzapine in Pediatric Patients With Schizophrenia or Bipolar I Disorder

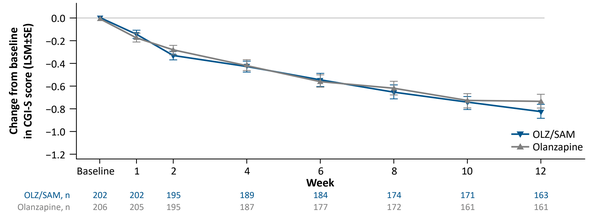
Lara Finlayson,[1] April Wurnitsch,[1] Alexandra Lovett,[1] David McDonnell[2]

[1]Alkermes, Inc., Waltham, MA, USA; [2]Alkermes Pharma Ireland Ltd., Dublin, Ireland

BACKGROUND

- Olanzapine is an effective treatment for schizophrenia and bipolar I disorder (BD-I)[1,2] but is associated with an increased risk of weight gain[3]; this risk may be greatest in pediatric patients[4,5]
- The combination of olanzapine and samidorphan (OLZ/SAM) was developed to provide the antipsychotic efficacy of olanzapine while mitigating weight gain associated with olanzapine[6]
- OLZ/SAM is approved for the treatment of adults with schizophrenia or BD-I, and it is being evaluated for the potential treatment of pediatric patients[7]
- In adult early-in-illness patients with schizophrenia, schizophreniform disorder, or BD-I, OLZ/SAM provided the antipsychotic efficacy of olanzapine (**Figure 1**) but with significantly less weight gain vs olanzapine monotherapy[8] (**Figure 2**)
  - Adverse events (AEs) were reported by 134/211 (63.5%) patients who received OLZ/SAM and 136/215 (63.3%) patients who received olanzapine
  - Most AEs were mild to moderate in severity; AEs reported by ≥10% of the OLZ/SAM and olanzapine groups were weight increase (21.8% and 25.6%, respectively) and somnolence (10.9% and 9.3%, respectively)
- ENLIGHTEN-Youth (ALKS3831-A312; ClinicalTrials.gov identifier NCT05303064) is an ongoing randomized double-blind trial of OLZ/SAM vs olanzapine evaluating weight gain as assessed by body mass index (BMI) Z score in pediatric patients with schizophrenia or BD-I

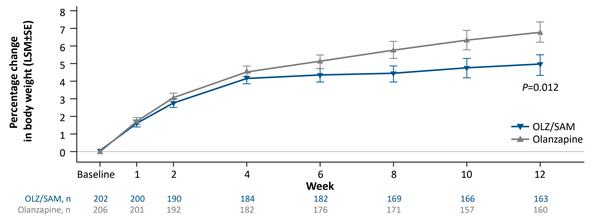
Figure 1. Changes From Baseline in CGI-S Score[a] at Week 12 in Adult Early-in-Illness[b] Patients With Schizophrenia, Schizophreniform Disorder, or BD-I



	Baseline	1	2	4	6	8	10	12
OLZ/SAM, n	202	202	195	189	184	174	171	163
Olanzapine, n	206	205	195	187	177	172	161	161

[a]Change from baseline in CGI-S score within the OLZ/SAM treatment group was a key secondary endpoint and was not formally tested due to early termination of the hierarchical testing procedure, which required statistical significance on the key secondary endpoint of proportion of patients with ≥10% weight gain before proceeding. [b]Patients aged 18 to <40 years (US sites: ≥16 to <40 years) and within 4 years from the initial onset of active symptoms.
BD-I, bipolar I disorder; CGI-S, Clinical Global Impressions–Severity; LSM, least squares mean; OLZ/SAM, combination olanzapine and samidorphan.

Figure 2. Percentage Changes From Baseline in Body Weight[a] by Visit in Adult Early-in-Illness[b] Patients With Schizophrenia, Schizophreniform Disorder, or BD-I



	Baseline	1	2	4	6	8	10	12
OLZ/SAM, n	202	200	190	184	182	169	166	163
Olanzapine, n	206	201	192	182	176	171	157	160

[a]The primary endpoint was percent change from baseline in body weight at week 12. [b]Patients aged 18 to <40 years (US sites: ≥16 to <40 years) and within 4 years from the initial onset of active symptoms.
BD-I, bipolar I disorder; LSM, least squares mean; OLZ/SAM, combination olanzapine and samidorphan.

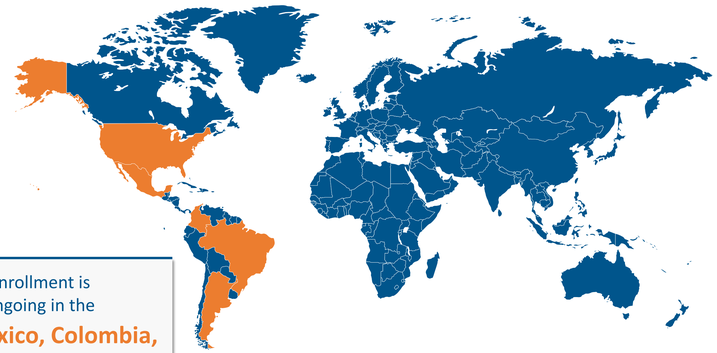
ENLIGHTEN-Youth

NCT05303064

The objective of this trial is to assess changes in BMI Z score following treatment with OLZ/SAM vs olanzapine in pediatric patients with schizophrenia or BD-I

Approximately **220 pediatric patients with schizophrenia or BD-I** are expected to be enrolled

Study Start Date: **June 30, 2022** → **September 2026**: Estimated Enrollment Completion Date



Enrollment is ongoing in the **US, Mexico, Colombia, Brazil,** and **Argentina**

Key eligibility criteria

- Aged 13–17 or 10–17 years with a diagnosis of schizophrenia or BD-I, respectively
- Able to receive outpatient care by study week 2
- Currently treated with olanzapine or another antipsychotic with inadequate treatment response

Key exclusion criteria

- BMI percentile >98th or <5th
- Diagnosis of diabetes mellitus or prediabetes laboratory results at screening (glycosylated hemoglobin ≥6%)
- Recent enrollment in a weight management program or major diet/exercise changes within 6 weeks of screening or planned enrollment in a weight management program during the study
- Major depressive episode (patients with BD-I) or comorbid neuropsychiatric disorder that could interfere with study participation
- Intolerance, allergy, or hypersensitivity to olanzapine or opioid antagonists
- Positive drug screen for opioids

Endpoints and outcome measures

Primary

- Change from baseline in BMI Z score at week 12

Key secondary

- Proportion of patients with a ≥0.5 increase from baseline in BMI Z score at week 12
- Time to all-cause study drug discontinuation over 52 weeks
- Change from baseline in waist circumference at week 12

Additional secondary

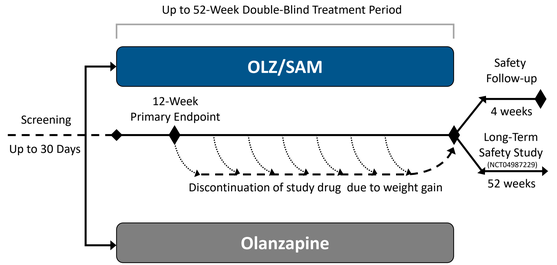
- Patients with schizophrenia: change from baseline in Positive and Negative Symptom Scale (PANSS) total score by visit at week 12
- Patients with BD-I: change from baseline in the Young Mania Rating Scale and Child Depression Rating Scale-Revised by visit at week 12
- Safety and tolerability, assessed based on AEs, weight and waist circumference changes, laboratory test results, vital signs, electrocardiograms, abnormal movement scales, and suicidal ideation and behavior

METHODS

Study design

- This is a multinational, multicenter, phase 3, randomized, double-blind, 52-week study comparing OLZ/SAM with olanzapine in pediatric patients with schizophrenia or BD-I
  - A screening period up to 30 days before randomization is followed by up to 52 weeks of treatment (**Figure 3**)
  - Those completing the randomized trial are eligible to enroll in a 52-week open-label extension study (ALKS3831-A313; ClinicalTrials.gov identifier NCT04987229) to evaluate the long-term safety/tolerability of OLZ/SAM
  - Patients completing the randomized trial who do not elect to continue in the long-term safety study enter a 4-week safety follow-up period

Figure 3. Study Design



OLZ/SAM, combination olanzapine and samidorphan.

- After the screening period, patients are randomized 1:1 to either OLZ/SAM (2.5–20/10 mg) or olanzapine (2.5–20 mg) orally once daily for up to 52 weeks
- For patients receiving OLZ/SAM, the starting dose of olanzapine will be 2.5 mg/day or 5 mg/day at the discretion of the investigator with a maximum daily dose of 20 mg/day; the starting dose of samidorphan will be 10 mg/day
- For patients receiving olanzapine alone, the starting dose of olanzapine will be 2.5 mg/day or 5 mg/day at the discretion of the investigator with a maximum daily dose of 20 mg/day
- Patients have biweekly visits after week 2 until week 12 and monthly visits thereafter until week 52
- All patients undergo 1 session of behavioral weight counseling at baseline
- Body weight and waist circumference are measured throughout the 52-week treatment period
- Patients with clinically significant weight gain (≥0.5 BMI Z-score increase) at week 12 and afterward will be discontinued from the study drug
  - Patients discontinuing the study drug due to weight gain are eligible to enroll in the 52-week open-label OLZ/SAM safety extension study or to otherwise enter the 4-week safety follow-up period

SUMMARY

- ENLIGHTEN-Youth will evaluate the effect of OLZ/SAM vs olanzapine on BMI Z score in pediatric patients with schizophrenia or BD-I and assess the safety/tolerability of OLZ/SAM in this population
- Information for patient referrals is available at: http://www.enlightenyouthstudy.com/hcp

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DISCLOSURES

LF, **AW**, and **AL** are or were employees of Alkermes, Inc., and may own stock/options in the company. **DM** is or was an employee of Alkermes Pharma Ireland Ltd., and may own stock/options in the company.

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