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

René S. Kahn [a,*], Bernard L. Silverman [b], Lauren DiPetrillo [b], Christine Graham [b], Ying Jiang [b], Jiani Yin [b], Adam Simmons [b], Vasudev Bhupathi [b], Bei Yu [b], Sergey Yagoda [b], Craig Hopkinson [b], David McDonnell [c]

[a] Icahn School of Medicine at Mount Sinai, New York, NY, USA
[b] Alkermes, Inc., Waltham, MA, USA
[c] Alkermes Pharma Ireland Limited, Dublin, Ireland
*Corresponding author

Introduction

- Olanzapine is a second generation antipsychotic and is effective for both acute and chronic treatment of schizophrenia.[1,2]
- The clinical utility of olanzapine is limited due to its association with weight gain and the development of conditions related to metabolic dysregulation, such as diabetes-related adverse effects (DRAEs) and hyperlipidemia. [2,3,4]
- Samidorphan is an opioid modulator with μ-antagonist properties. [5]
- Concomitant administration of olanzapine and samidorphan (OLZ/SAM):
  - Mitigates olanzapine-associated weight gain and metabolic dysregulation in preclinical and clinical trials. [6,7,8]
  - Reduces schizophrenia-related symptoms in phase 2 and 3 clinical trials to a similar extent as olanzapine monotherapy. [7,8,9]
- **Objective of ENLIGHTEN-2 long term extension:** Determine the long term safety and tolerability of OLZ/SAM treatment in adults with schizophrenia.

1. Kishimoto T, et al. World Psychiatry 2019; 18(2): 208-224. **2.** Lieberman JA, et al. N. Engl. J. Med. 2005; 353(12): 1209-1223. **3.** Baker RA, et al. Psychopharmacol. Bull. 2009; 42(1): 11-31. **4.** Koro CE, et al. Arch. Gen. Psychiatry 2002; 59(11): 1021-1026. **5.** Shram MJ, et al. J. Clin. Psychopharmacol. 2015; 35(3): 242-249. **6.** Cunningham JI, et al. J. Psychopharmacol. 2019; 33(10): 1303-1316. **7.** Martin WF, et al. Am. J. Psychiatry 2019; 176(6): 457-467. **8.** Correll CU, et al. Am. J. Psychiatry 2020; 177(12): 1168-1178. **9.** Potkin SG, et al. J. Clin. Psychiatry 2020; 81(2): e1-e9.

DRAEs=Diabetes-Related Adverse Effects; OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

ENLIGHTEN-2 long-term extension: Study Design

Preceding Study

ELIGHTEN-2

Objective: Evaluate patient weight gain with OLZ/SAM treatment compared to olanzapine in adults with schizophrenia.

Study Type	Interventional
Enrollment	561 participants
Allocation	Randomized
Intervention Model	Parallel Assignment
Masking	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Study Start	March 2016
Study Completion	November 2018

Key Inclusion Criteria:

- 18-55 years of age
- Primary diagnosis of schizophrenia
- Baseline BMI between 18 and 30

ClinicalTrials.gov identifier: NCT02694328

Within 7 days of ELIGHTEN-2 completion

Current Study

ENLIGHTEN-2-EXT

Objective: Determine the long term safety and tolerability of OLZ/SAM treatment in adults with schizophrenia.

Study Type	Interventional
Enrollment	266 participants, subgroup of ENLIGHTEN-2
Allocation	N/A
Intervention Model	Single Group Assignment
Masking	None (Open Label)
Study Start	August 2016
Study Completion	October 2019

Initial olanzapine dosage based on dose received at the conclusion of ENLIGHTEN-2. Samidorphan dose held constant. Possible initial dosing:

- OLZ/SAM 10/10 mg
- OLZ/SAM 15/10 mg
- OLZ/SAM 20/10 mg

ClinicalTrials.gov identifier: NCT02873208

Safety follow-up (4 weeks)

Follow-up extension study (up to 4 years)

OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

Demographics and baseline disease characteristics

Parameter	All patients (*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/m2	26.8 (3.8)
PANSS total score, mean (SD)	59.0 (11.8)
CGI-S score, mean (SD)	3.1 (0.7)

- Patients who completed the ENLIGHTEN-2 clinical trial were eligible to participate in ENLIGHTEN-2-EXT if a clinical provider determined they were likely to benefit from continued OLZ/SAM treatment.

- Key exclusion criteria for ENLIGHTEN-2-EXT:
  - Use of medications contraindicated with olanzapine.
  - Use of prohibited drugs.
  - Females who were pregnant or nursing.

SD= Standard Deviation; BMI=Body Mass Index; PANSS= Positive and Negative Syndrome Scale; CGI-S= Clinical Global Impression-Severity; OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

Methods for Safety, Tolerability, and Efficacy Evaluation

- Safety and tolerability assessments:
  - Adverse event (AE) monitoring
  - Weight and waist circumference measurements
  - Clinical laboratory testing
  - Vital signs
  - 12-lead electrocardiograms (ECGs)
  - Movement disorder rating scales
    - Abnormal Involuntary Movement Scale (AIMS)
    - Barnes Akathisia Rating Scale (BARS)
    - Simpson-Angus Scale (SAS)
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Long-term OLZ/SAM efficacy assessments:
  - Positive and Negative Syndrome Scale (PANSS)
  - Clinical Global Impression-Severity (CGI-S)
- Safety, tolerability, and efficacy values were compared to the baseline measurements recorded at the first OLZ/SAM treatment administered for the extension study.

AE= Adverse Event; ECG= Electrocardiogram; AIMS= Abnormal Involuntary Movement Scales; BARS= Barnes Akathisia Rating Scale; SAS= Simpson-Angus Scale; C-SSRS= Columbia-Suicide Severity Rating Scale; PANSS= Positive and Negative Syndrome Scale; CGI-S= Clinical Global Impression-Severity; OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

Safety and Tolerability

Adverse events summary (baseline to week 52)

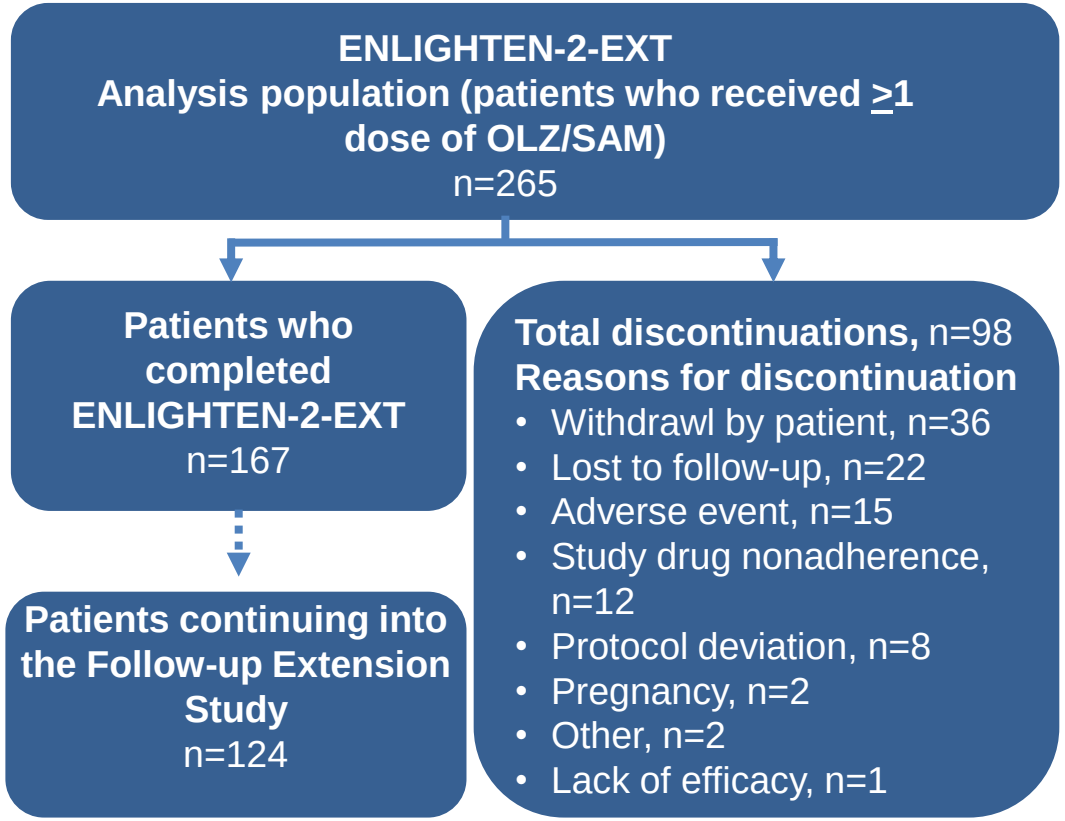
Patients, n (%)	All patients (N = 265)
Any AE	161 (60.8)
By highest severity	
Mild	93 (35.1)
Moderate	61 (23.0)
Severe	7 (2.6)
AE leading to treatment discontinuation	15 (5.7)
AEs reported in ≥2% of patients	
Weight decreased	23 (8.7)
Extra dose administered	21 (7.9)
Headache	18 (6.8)
Weight increased	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)

- Changes in serum chemistries, hematological parameters, vital signs and ECG were generally minimal.
- In patients with normal prolactin levels at baseline, 27.4% of females and 13.6% of males had prolactin levels that exceeded normal ranges at least once during treatment.
- Extrapyramidal symptoms were not common.
  - 7 patients experienced AEs possibly related to extrapyramidal symptoms, but continued treatment.
- There were no reported suicides.

AE= Adverse Event; ECG= Electrocardiogram; OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

Safety and Tolerability

Patient Disposition



Adverse events leading to discontinuation:

- Blood prolactin increase, blood triglycerides increase, dizziness, electrocardiogram T wave abnormality, GGT increase, diabetes mellitus, nausea, pulmonary embolism, sedation, seizure and somnolence (*n* = 1 each)
- Psychotic disorder (*n* = 2)
- Glycosylated hemoglobin increased (*n* = 3)

Baseline Patient Characteristics

Completed	Discontinued
n = 167	n = 98
73.7% male	70.4% male
69.5% black	72.5% black
41.4 years old	39.3 years old
80.9 kg	80.2 kg
58.8 PANSS	59.5 PANSS

Baseline demographics and clinical characteristics were similar among individuals who completed or discontinued the study.

OLZ/SAM= Olanzapine and Samidorphan Combination Therapy; PANSS= Positive and Negative Syndrome Scale; GGT= gamma-glutamyltransferase

Metabolic Assessment

Body weight and waist circumference remained stable throughout the 52 week study.

- The mean (SD) change in body weight from baseline to week 52 was -0.3 (6.22) kg.
- The mean (SD) change in waist circumference among patients was -0.35 (6.12) cm.

Fasting cholesterol and triglyceride levels were stable with small net decreases.

- Less than 4% of patients experienced sustained changes in cholesterol or triglycerides.

HbA1c and fasting insulin concentrations indicated glycemic control was maintained with long-term OLZ/SAM treatment.

- 11% of patients experienced sustained elevated HbA1c.
- 0.4% of patients experienced sustained elevated fasting glucose.

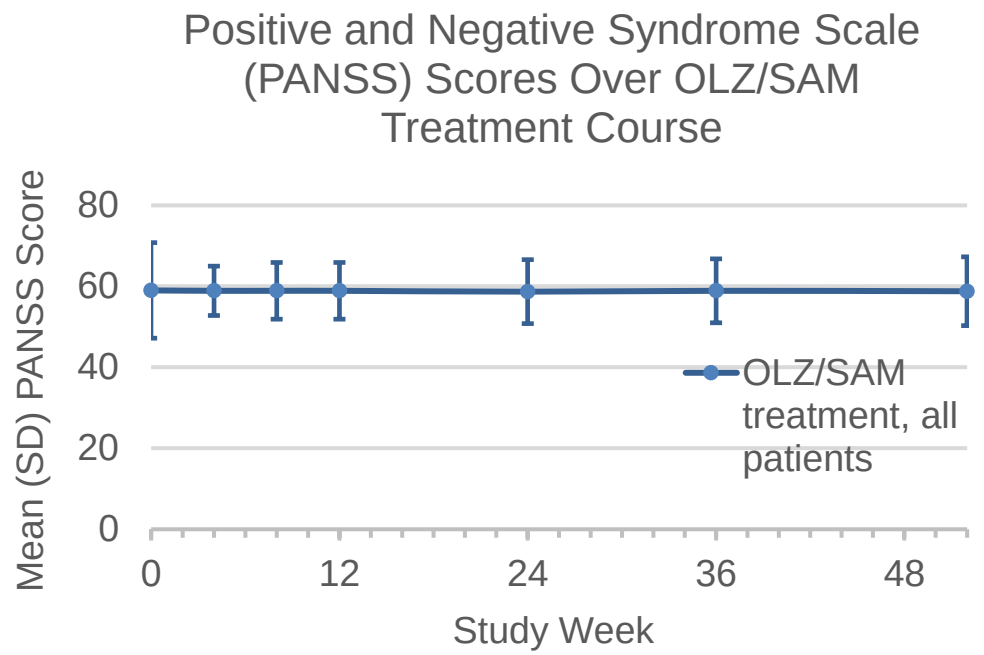
Anytime or sustained potentially clinically significant (PCS) value shifts in fasting lipid and glycemic parameters from baseline to week 52

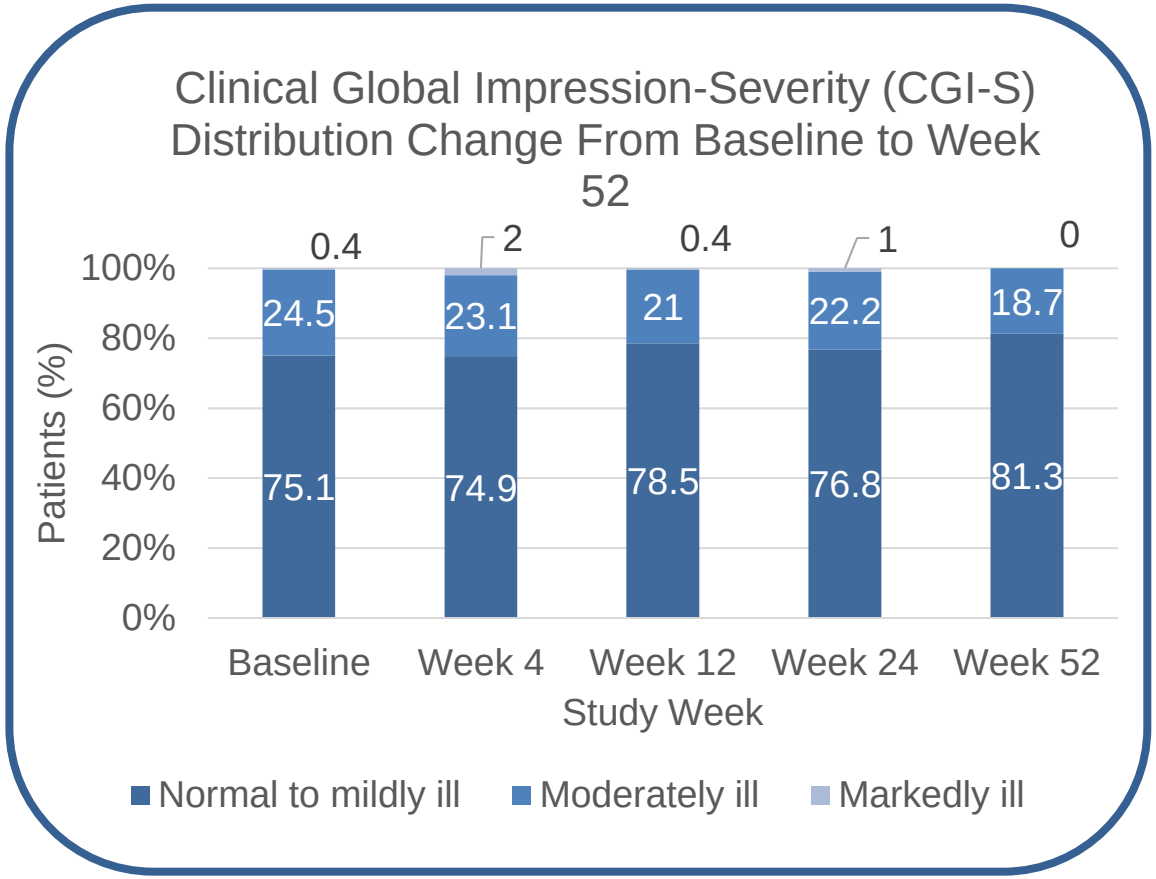
Shift category	Anytime, all patients, n/m (%)	Sustained, all patients, n/m (%)
Glucose <126 to ≥126 mg/dL	29/254 (11.4)	1/229 (0.4)
HbA1c <5.7% to ≥5.7%	49/174 (28.2)	17/154 (11.0)
Total cholesterol <240 mg/dL to ≥240 mg/dL	24/238 (10.1)	1/217 (0.5)
HDL cholesterol ≥40 mg/dL to <40 mg/dL	33/215 (15.3)	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)

Anytime=Patients meeting PCS shift at any postbaseline visit.
Sustained= Patients meeting PCS shift at two consecutive postbaseline visits.
n= patients who met the shift category
m= patients with a non potentially clinically significant baseline and ≥2 postbaseline assessments

SD= Standard Deviation; HbA1c= glycosylated hemoglobin; HDL= High Density Lipoprotein; LDL= Low Density Lipoprotein; OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

Long-term durability of OLZ/SAM treatment effect





OLZ/SAM provided sustained management of schizophrenia symptoms.

PANSS= Positive and Negative Syndrome Scale; CGI-S= Clinical Global Impression-Severity; OLZ/SAM= Olanzapine and Samidorphan Combination Therapy

Conclusions

- Bodyweight and metabolic markers were generally stable throughout the 52 week OLZ/SAM treatment period.
- Schizophrenia symptoms were well managed by OLZ/SAM over 52 weeks.
- Future evaluation of the metabolic impact of OLZ/SAM should involve real-world data from large populations and long-term follow-up.
- ENLIGHTEN-2-EXT results do not directly generalize to patients with acute schizophrenia exacerbations.
- OLZ/SAM combination therapy is a promising long-term schizophrenia treatment option, which provides a similar antipsychotic efficacy to olanzapine alone, but with reduced weight gain and adverse metabolic effects.

OLZ/SAM= Olanzapine and Samidorphan Combination Therapy