Safety, Tolerability, and Durability of Treatment Effect of Olanzapine and Samidorphan: A Patient Subgroup Analysis of a 4-Year Open-Label Study

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BACKGROUND

- A combination of olanzapine and samidorphan is approved in the US for the treatment of adults with schizophrenia or bipolar I disorder (BD-I)[1]
- In a 4-year open-label study, OLZ/SAM treatment maintained symptom control and was associated with small changes in body weight and minimal changes in waist circumference in patients with schizophrenia, schizophreniform disorder, or BD-I[2]

OBJECTIVE

- To analyze OLZ/SAM's safety, tolerability, and durability of treatment effect across subgroups in a 4-year open-label study of adults with schizophrenia, schizophreniform disorder, or BD-I

METHODS

- The study (NCT03201757) was a phase 3, 2- to 4-year (48 month), multicenter, open-label study assessing the safety, tolerability, and durability of treatment effect of OLZ/SAM
- Eligible patients enrolled ≤7 days after completing 1 of 3 antecedent studies in the ENLIGHTEN clinical trial program
- Patients could receive ≥2 and up to 4 years of additional OLZ/SAM treatment
- Prespecified subgroup analyses were conducted by age (18–29 or ≥30 years), sex (male or female), race (Black/African American or non-Black/African American), baseline body mass index (BMI; <25 or ≥25 kg/m^2), and geographic region (US or non-US)
- Safety assessments included changes from baseline in body weight and waist circumference and incidences of adverse events (AEs)
- Durability of treatment effect was assessed with the Clinical Global Impression–Severity (CGI-S) scale

RESULTS

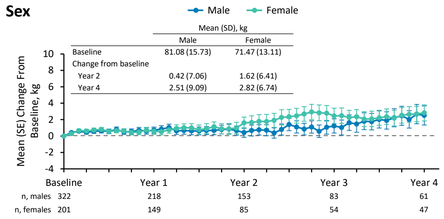
- Overall, 524 patients were enrolled and 523 received ≥1 dose of study drug (**Table 1**)
- Across subgroups, OLZ/SAM treatment was associated with small changes from baseline in body weight (**Figure 1**) and minimal changes in waist circumference (**Figure 2**) at 2 and 4 years
- Most AEs were mild or moderate in severity (**Table 2**); no clinically meaningful subgroup differences in AEs were observed
- Mean CGI-S scores remained stable across subgroups at 2 and 4 years (**Figure 3**)

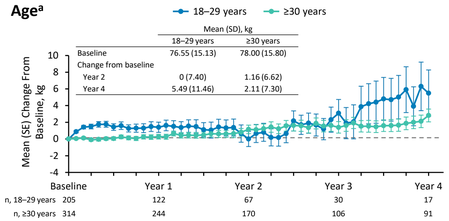
Table 1. Demographics and Baseline Clinical Characteristics[a]

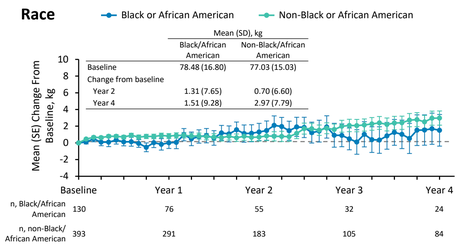
Characteristics	Subgroups									
	Sex		BMI		Age[b]		Geographic region		Race	
	Male (n=322)	Female (n=201)	<25 kg/m^2 (n=241)	≥25 kg/m^2 (n=282)	18-29 years (n=205)	≥30 years (n=314)	US (n=206)	Non-US (n=317)	Black/ African American (n=130)	Non-Black/ African American (n=393)
Age,[c] mean (SD), years	33.2 (11.7)	38.1 (12.4)	33.1 (11.9)	36.8 (12.2)	23.4 (3.2)	42.9 (9.2)	35.9 (12.4)	34.6 (12.0)	37.1 (12.1)	34.4 (12.1)
Sex, n (%)										
Male	322 (100)	0	160 (66.4)	162 (57.4)	154 (75.1)	167 (53.2)	144 (69.9)	178 (56.2)	86 (66.2)	236 (60.1)
Female	0	201 (100)	81 (33.6)	120 (42.6)	51 (24.9)	147 (46.8)	62 (30.1)	139 (43.8)	44 (33.8)	157 (39.9)
Race, n (%)										
White	226 (70.2)	154 (76.6)	174 (72.2)	206 (73.0)	153 (74.6)	226 (72.0)	68 (33.0)	312 (98.4)	0	380 (96.7)
Black or African American	82 (25.5)	44 (21.9)	55 (22.8)	71 (25.2)	40 (19.5)	83 (26.4)	125 (60.7)	1 (0.3)	126 (96.9)	0
Asian	6 (1.9)	2 (1.0)	6 (2.5)	2 (0.7)	7 (3.4)	1 (0.3)	5 (2.4)	3 (0.9)	0	8 (2.0)
Other[d]	8 (2.5)	1 (0.5)	6 (2.5)	3 (1.1)	5 (2.4)	4 (1.3)	8 (3.9)	1 (0.3)	4 (3.1)	5 (1.3)
Region, n (%)										
US	144 (44.7)	62 (30.8)	87 (36.1)	119 (42.2)	81 (39.5)	121 (38.5)	206 (100)	0	128 (98.5)	78 (19.8)
Non-US	178 (55.3)	139 (69.2)	154 (63.9)	163 (57.8)	124 (60.5)	193 (61.5)	0	317 (100)	2 (1.5)	315 (80.2)
Weight, mean (SD), kg	81.1 (15.7)	71.5 (13.1)	66.8 (9.1)	86.4 (14.0)	76.6 (15.125)	78.0 (15.797)	79.4 (16.9)	76.1 (14.4)	78.5 (16.8)	77.0 (15.0)
BMI, mean (SD), kg/m^2	25.8 (4.1)	26.3 (4.7)	22.4 (2.0)	29.1 (3.3)	25.3 (4.0)	26.4 (4.5)	26.4 (4.3)	25.8 (4.3)	26.1 (4.2)	26.0 (4.4)
CGI-S score, mean (SD)	3.11 (0.85)	2.98 (0.89)	3.08 (0.84)	3.04 (0.89)	3.03 (1.00)	3.08 (0.77)	2.95 (0.75)	3.14 (0.93)	3.00 (0.70)	3.08 (0.91)

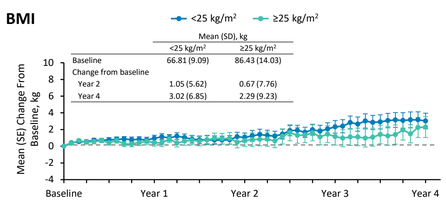
[a]All patients who received ≥1 dose of OLZ/SAM.
[b]Excluding 4 patients <18 years old.
[c]Age is based on data collected at the time of screening in the patient's initial randomized controlled trial.
[d]"Other" includes patients who were American Indian or Alaska Native individuals, those reporting multiple races, and those responding "other."
BMI, body mass index; CGI-S, Clinical Global Impression–Severity; OLZ/SAM, combination olanzapine and samidorphan.

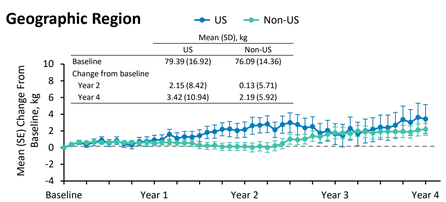
Figure 1. Changes From Baseline in Body Weight





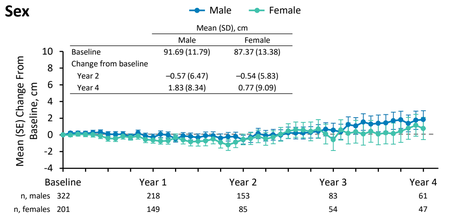


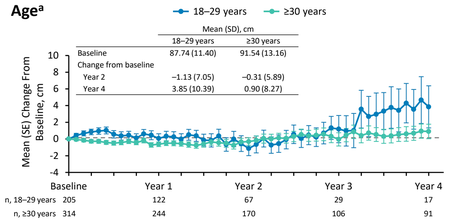


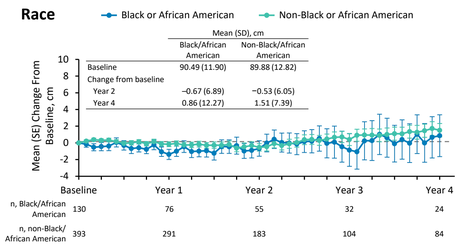


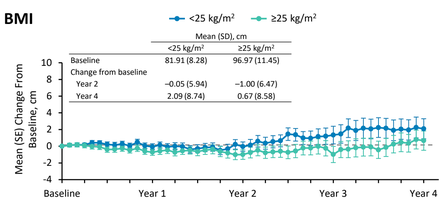
[a]Excluding 4 patients <18 years old.
BMI, body mass index.

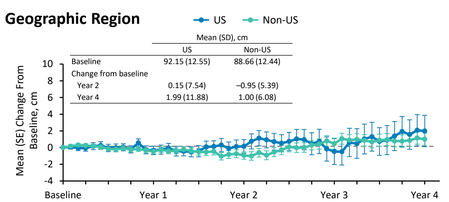
Figure 2. Changes From Baseline in Waist Circumference





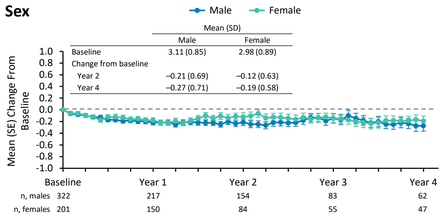


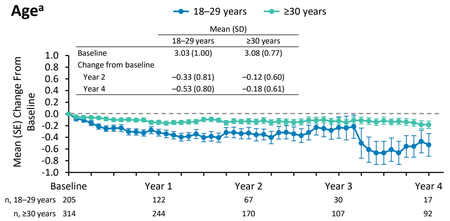


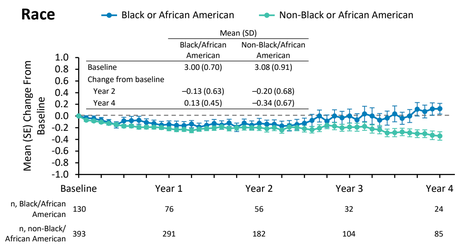


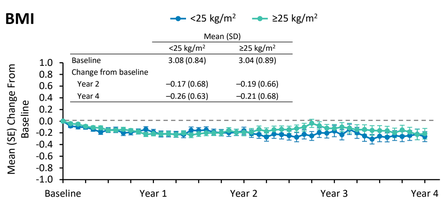
[a]Excluding 4 patients <18 years old.
BMI, body mass index.

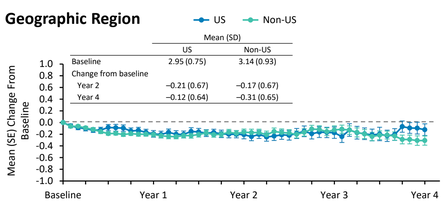
Figure 3. Changes From Baseline in CGI-S Score











[a]Excluding 4 patients <18 years old.
BMI, body mass index; CGI-S, Clinical Global Impression–Severity.

Table 2. Summary of Adverse Events[a]

Category[b]	All Patients (N=523)
Any AE, n (%)	314 (60.0)
AEs by highest severity, n (%)	
Mild	143 (27.3)
Moderate	148 (28.3)
Severe	23 (4.4)
AEs leading to discontinuation	44 (8.4)
Any SAE	35 (6.7)
SAEs leading to death[c]	1 (0.2)
Most common AEs (≥5% of patients)	
Weight increased	51 (9.8)
Headache	37 (7.1)
Anxiety	32 (6.1)
Insomnia	31 (5.9)
Somnolence	31 (5.9)
Nausea	30 (5.7)
Weight decreased	30 (5.7)

[a]All patients who received ≥1 dose of OLZ/SAM.
[b]Patients who experienced >1 AE in a category were counted only once in that category.
[c]One SAE resulted in death during the study (completed suicide); the investigator assessed this event as not related to study treatment.
AE, adverse event; OLZ/SAM, combination of olanzapine and samidorphan; SAE, serious adverse event.

LIMITATIONS

- The lack of a comparator arm may limit interpretation of safety and efficacy data
- Missing data due to patients who discontinued may have affected the results
- Patients with a less favorable outcome may have dropped out of the antecedent trial, creating potential selection bias
- The baseline characteristics of patients in this study may have varied due to differences in the inclusion and exclusion criteria of the 3 antecedent studies

CONCLUSIONS

- Outcomes after up to 4 years of additional OLZ/SAM treatment were generally similar across age, sex, race, BMI, and geographic subgroups
- The safety profile of OLZ/SAM across these subgroups was generally consistent with the previously published overall study results[2]

REFERENCES

1. Lybalvi [package insert]. Waltham, MA: Alkermes, Inc.; 2024.
2. Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511. DOI: 10.4088/JCP.24m15511

DISCLOSURES

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CA, MD, 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.
CUC has been a consultant and/or advisor for or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Jamjoom Pharma, Janssen/Johnson & Johnson, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, MindPax, Mitsubishi Tanabe Pharma, Mylan, Neurelis, Neurocrine, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka; has served on a data safety monitoring board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva; has received grant support from Janssen and Takeda; has received royalties from UpToDate; and is a stock option holder of Cardio Diagnostics, Kūleon Biosciences, LB Pharma, MedLink, MindPax, Quantic, and Terran.

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