Olanzapine/Samidorphan Effects on Weight Gain: A Meta-analysis of Phase 2 and 3 Randomized, Double-Blind Studies

Christoph Correll, MD,[1-3] Michael J. Doane, PhD,[4] David McDonnell, MD,[5] Meihua Wang, PhD,[4] Sarah Akerman, MD,[4] S. Stephen R. Saklad, PharmD, BCPP[6]

[1]Zucker Hillside Hospital, Glen Oaks, NY, USA; [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [3]Charité Universitätsmedizin, Berlin, Germany; [4]Alkermes, Inc., Waltham, MA, USA; [5]Alkermes Pharma Ireland Ltd., Dublin, Ireland; [6]The University of Texas at Austin, College of Pharmacy, Pharmacotherapy Division, San Antonio, TX, USA

INTRODUCTION

- Olanzapine has established antipsychotic efficacy in the treatment of schizophrenia (SZ) and bipolar I disorder (BD-I)[1,2]
- Associated weight gain and metabolic sequelae, however, have limited olanzapine's clinical use[1,3]
- Olanzapine/samidorphan (OLZ/SAM; Lybalvi, Alkermes, Inc.) is approved in the United States for the treatment of adults with SZ or BD-I[4]
- OLZ/SAM was designed to maintain the established antipsychotic efficacy of olanzapine while mitigating weight gain
- In clinical trials, OLZ/SAM was consistently associated with less weight gain than was olanzapine[5-7]

OBJECTIVE

- To evaluate the weight-change profile of OLZ/SAM versus that of olanzapine in patients with SZ or BD-I after 12 weeks of treatment
  - To characterize the overall weight-mitigation effect of OLZ/SAM versus olanzapine in 3 similarly designed clinical trials (1 phase 2 and 2 phase 3 studies)

METHODS

Study Design

- A meta-analysis was conducted using individual patient data from 3 studies (1 phase 2 and 2 phase 3 randomized, double-blind clinical trials) in which change in body weight was a primary or secondary endpoint (**Table 1**)

TABLE 1. Overview of Clinical Trials Included in the Analysis

Study	Phase	ClinicalTrials.gov Identifier	Duration, weeks	Population	Patients Randomized or Enrolled, n
Martin et al, 2019[5]	2	NCT01903837	12	Adults with SZ	347
Correll et al, 2020[6]	3	NCT02694328	24	Adults with SZ	561
Kahn et al, 2022[7]	3	NCT03187769	12	Young adults with SZ, BD-I, or schizophreniform disorder who were early in the course of illness	428

BD-I, bipolar I disorder; SZ, schizophrenia.

- All patients pooled for analysis were aged ≥18 years and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, or *Fifth Edition* criteria for SZ or BD-I
- Only patients initially diagnosed with schizophreniform disorder who were subsequently diagnosed with SZ or BD-I by week 12 were included in these analyses
- Only patients receiving daily OLZ/SAM (olanzapine 5–20 mg + samidorphan 10 mg) or olanzapine (5–20 mg) who had ≥1 postbaseline weight assessment by week 12 were analyzed
  - Patients taking fixed-dose OLZ/SAM combinations containing 5 or 20 mg of samidorphan were not analyzed
- In each study, eligible patients were required to have a body mass index of ≤30 kg/m^2

Outcomes

- The primary outcome was percent change from baseline body weight at week 12, analyzed using an individual patient data mixed model for repeated measures approach
- Secondary outcomes included the proportions of patients with clinically significant weight gain of ≥7% or ≥10% from baseline at week 12, analyzed using a generalized linear mixed model
- Additional outcomes at week 12 included antipsychotic efficacy as assessed by Clinical Global Impressions-Severity of Illness (CGI-S) score, as well as rates of adverse events and metabolic parameter changes

RESULTS

- Of the 1336 patients randomized in the 3 studies, 1063 (80%) patients met inclusion criteria and had ≥1 postbaseline weight assessment by week 12 (NCT01903837, n=161; NCT02694328, n=538; NCT03187769, n=364)

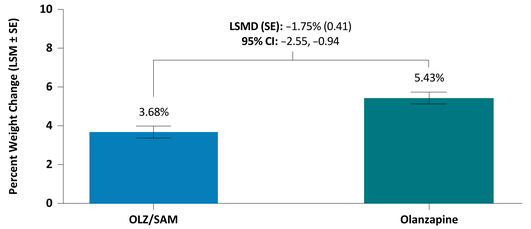
TABLE 2. Demographic and Baseline Characteristics

Parameters	OLZ/SAM (N=532)	Olanzapine (N=531)	All Patients (N=1063)
Baseline CGI-S, mean (SD)	3.54 (0.7)	3.61 (0.7)	3.58 (0.7)
Age, mean (SD), years	35.2 (10.6)	35.2 (10.9)	35.2 (10.7)
Sex, n (%)			
Male	379 (71.2)	376 (70.8)	755 (71.0)
Female	153 (28.8)	155 (29.2)	308 (29.0)
Race, n (%)			
Black	287 (53.9)	282 (53.1)	569 (53.5)
White	223 (41.9)	217 (40.9)	440 (41.4)
Asian	8 (1.5)	14 (2.6)	22 (2.1)
American Indian or Alaska Native	4 (0.8)	3 (0.6)	7 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.2)	2 (0.4)	3 (0.3)
Other	3 (0.6)	4 (0.8)	7 (0.7)
Multiracial	6 (1.1)	9 (1.7)	15 (1.4)
Baseline BMI, mean (SD), kg/m^2	24.8 (3.3)	24.9 (3.4)	24.8 (3.3)
Region, n (%)			
United States	416 (78.2)	417 (78.5)	833 (78.4)
Outside the United States	116 (21.8)	114 (21.5)	230 (21.6)

BMI, body mass index; OLZ/SAM, olanzapine combined with samidorphan.

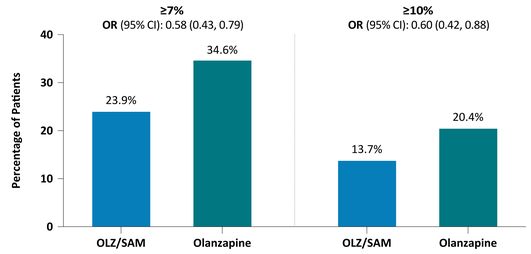
Weight Efficacy

FIGURE 1. Percent Change in Body Weight at Week 12



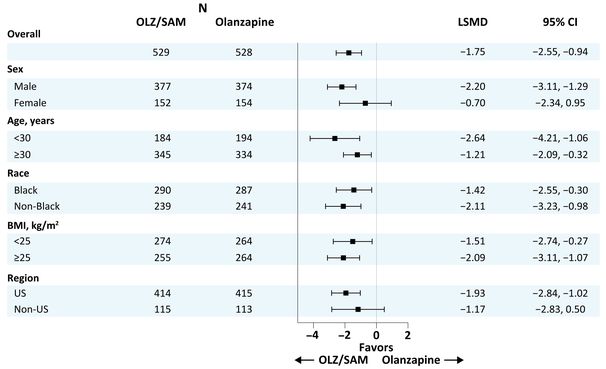
LSM, least-squares mean; LSMD, least-squares mean difference; OLZ/SAM, olanzapine combined with samidorphan.

FIGURE 2. Proportions of Patients With ≥7% or ≥10% Change in Body Weight at Week 12



OLZ/SAM, olanzapine combined with samidorphan; OR, odds ratio.

FIGURE 3. Subgroup Analysis of Percent Change in Body Weight at Week 12



BMI, body mass index; LSMD, least-squares mean difference; OLZ/SAM, olanzapine combined with samidorphan.

Antipsychotic Efficacy

- Mean (SD) changes from baseline in CGI-S score were −0.41 (0.7) for OLZ/SAM and −0.42 (0.7) for olanzapine

Safety and Tolerability

TABLE 3. Summary of Adverse Events Occurring in ≥5% of Patients

AE, n (%)	OLZ/SAM (N=548)	Olanzapine (N=544)
Any	352 (64.2)	360 (66.2)
Weight increased	106 (19.3)	133 (24.4)
Somnolence	87 (15.9)	68 (12.5)
Dry mouth	45 (8.2)	27 (5.0)
Appetite increased	40 (7.3)	49 (9.0)
Waist circumference increased	23 (4.2)	32 (5.9)

AE, adverse event; OLZ/SAM, olanzapine combined with samidorphan.

Metabolic Parameter Changes

- Changes in metabolic parameters were small and similar for OLZ/SAM and olanzapine after 12 weeks of treatment

TABLE 4. Change From Baseline in Metabolic Parameters at Week 12

Parameter	OLZ/SAM (N=415), mean (SD)	Olanzapine (N=425), mean (SD)
Glucose,[a] mg/dL	4.2 (21.3)	1.9 (14.0)
HbA_{1c},[b] %	0 (0.4)	0 (0.3)
Total cholesterol, mg/dL	4.2 (29.5)	7.1 (29.6)
HDL cholesterol, mg/dL	−3.5 (12.1)	−3.4 (12.2)
LDL cholesterol, mg/dL	6.0 (26.6)	7.2 (25.0)
Triglycerides, mg/dL	15.4 (78.7)	20.7 (70.8)

[a]For change from baseline to week 12, n=383 (OLZ/SAM) and n=388 (olanzapine). [b]For change from baseline to week 12, n=411 (OLZ/SAM) and n=418 (olanzapine).
HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLZ/SAM, olanzapine combined with samidorphan.

LIMITATIONS

- This analysis assessed only short-term effects of OLZ/SAM versus those of olanzapine
- The study was not designed to make statistical comparisons between OLZ/SAM and olanzapine on antipsychotic efficacy, adverse events, or metabolic parameter changes
- These results may not be generalizable to the larger population of patients with SZ or BD-I

CONCLUSIONS

- In this individual patient data meta-analysis of 3 clinical trials, OLZ/SAM resulted in less weight gain than olanzapine after 12 weeks of treatment
  - Results consistently favored OLZ/SAM for percent change in weight, as well as for the risk of experiencing clinically significant weight gain of ≥7% or ≥10%
- Numerically, OLZ/SAM resulted in a lower percent change in body weight across all subgroups examined
  - These results suggest that OLZ/SAM mitigates olanzapine-associated weight gain across a broad range of patient demographics, including age, sex, and race, among other characteristics
- Both OLZ/SAM and olanzapine were associated with small and similar changes in metabolic parameters across 12 weeks, despite differences in weight gain
  - The 12-week duration of treatment in this analysis may have been too short to detect changes in metabolic risk factors associated with weight gain that develop in the long-term
- In general, treatment with olanzapine has been associated with metabolic worsening and an increased risk of developing metabolic syndrome,[8,9] whereas in a post-hoc analysis of NCT02694328, OLZ/SAM demonstrated a significant reduction in the risk of metabolic syndrome and hypertension in patients free of those conditions at baseline[10]
  - Furthermore, the small metabolic parameter changes observed in NCT02694328 remained stable over an additional 52 weeks of OLZ/SAM treatment in the associated open-label extension study
- After 12 weeks of treatment, there was an improvement in disease severity based on CGI-S scores; similar improvements were observed for OLZ/SAM- and olanzapine-treated patients
  - These results are consistent with other clinical trial results in which OLZ/SAM treatment resulted in antipsychotic efficacy that was comparable to that of olanzapine[11]

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AUTHOR DISCLOSURES

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M.J. Doane, **M. Wang**, and **S. Akerman** are or were employees of Alkermes, Inc., and may own stock/options in the company.

D. McDonnell is an employee of Alkermes Pharma Ireland Ltd. and may own stock/options in the company.

S.R. Saklad is an employee of The University of Texas at Austin College of Pharmacy; was appointed to the Texas Health and Human Services Commission, San Antonio State Hospital, and the UT Health San Antonio Long School of Medicine; has served as consultant for Alkermes, Genomind, Janssen, Karuna, and Otsuka; has participated on the speakers bureau for Neurocrine, Otsuka PsychU, Teva, Texas Society of Health-System Pharmacists, and, on occasion, for several professional organizations; serves on the Business Development Council for the American Association of Psychiatric Pharmacists; and has served as expert witness on both defendant and plaintiff sides. He has no direct stock ownership in any pharmaceutical corporation.

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