

# An Evidence-Based Review of OLZ/SAM for Treatment of Adults with Schizophrenia or Bipolar I Disorder

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**Abstract:** Olanzapine effectively treats schizophrenia and bipolar I disorder (BD-I); however, its use is limited by the risk of significant weight gain and metabolic effects. OLZ/SAM, a combination of olanzapine and samidorphan, was recently approved in the United States for the treatment of adults with schizophrenia or BD-I. OLZ/SAM provides the efficacy of olanzapine while mitigating olanzapine-associated weight gain through opioid-receptor blockade. Here, we summarize OLZ/SAM clinical data characterizing pharmacokinetics, antipsychotic efficacy, weight mitigation efficacy, safety, and long-term treatment effects. In an acute exacerbation of schizophrenia, OLZ/SAM and olanzapine provided similar symptom improvements versus placebo at week 4. In stable outpatients with schizophrenia, OLZ/SAM treatment resulted in significantly less weight gain, reducing the risk for clinically significant weight gain and waist circumference increases of  $\geq 5$  cm by half, compared with olanzapine at week 24. Based on open-label extension studies, OLZ/SAM is safe and well tolerated for up to 3.5 years of treatment, while maintaining schizophrenia symptom control and stabilizing weight. The olanzapine component of OLZ/SAM was bioequivalent to branded olanzapine (Zyprexa); adjunctive OLZ/SAM had no clinically significant effects on lithium or valproate pharmacokinetics. Additionally, OLZ/SAM had no clinically relevant effect on electrocardiogram parameters in a dedicated thorough QT study. Overall, safety and tolerability findings from clinical studies with OLZ/SAM indicate a similar safety profile to that of olanzapine, with the exception of less weight gain. As OLZ/SAM contains the opioid antagonist samidorphan, it is contraindicated in patients using opioids and in those undergoing acute opioid withdrawal. Clinical trial results from more than 1600 subjects support the use of OLZ/SAM as a new treatment option for patients with schizophrenia or BD-I.

**Keywords:** antipsychotic agents, clinical efficacy, olanzapine, opioid antagonists, safety, weight gain

## Plain Language Summary

Antipsychotic choice for individuals with schizophrenia or bipolar I disorder (BD-I) requires balancing efficacy with tolerability. For example, while olanzapine is highly efficacious, it is associated with weight gain and/or changes in how the body regulates glucose and lipids. Since the body's natural opioid system is involved in regulating weight and metabolism, combining samidorphan with olanzapine is a potential strategy to address olanzapine-associated weight and metabolic side effects. We summarize clinical data for OLZ/SAM, a combination of olanzapine and the opioid receptor-blocking compound samidorphan, recently approved in the United States for the treatment of adults with schizophrenia or BD-I. In pharmacokinetic studies, plasma concentrations of olanzapine were similar when

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administered as OLZ/SAM or as the branded product, Zyprexa, with dose-proportional increases in concentration with increasing doses. Adjunctive OLZ/SAM did not affect lithium or valproate pharmacokinetics. Samidorphan's pharmacokinetic profile supports once-daily dosing in combination with olanzapine as OLZ/SAM. In clinical studies, OLZ/SAM provided similar antipsychotic efficacy as olanzapine in patients with schizophrenia, with sustained symptom control during long-term treatment. OLZ/SAM treatment resulted in significantly less weight gain versus olanzapine; weight remained stable with long-term treatment. The safety profile of OLZ/SAM was generally consistent with that of olanzapine, except for less weight gain. Owing to samidorphan's opioid antagonist effects, OLZ/SAM is contraindicated in patients using opioids or undergoing acute opioid withdrawal. Lastly, because antipsychotic-associated weight gain is independent of disease state, OLZ/SAM provides a new treatment option for patients with either schizophrenia or BD-I that balances efficacy with a reduced risk of weight gain.

## Introduction

Schizophrenia and bipolar I disorder (BD-I) are chronic, complex psychiatric illnesses associated with substantial functional impairment and disability,<sup>1-3</sup> high rates of comorbid conditions,<sup>4,5</sup> and a high risk of suicide.<sup>6,7</sup> Both are associated with lower life expectancy, attributable in part to causes such as suicide, but also to higher rates of cardiovascular comorbidities.<sup>5,8,9</sup> While antipsychotics are the cornerstone of treatment in schizophrenia, and second-generation antipsychotics are commonly prescribed in the treatment of BD-I either as monotherapy or in combination with mood stabilizers,<sup>10,11</sup> they are often accompanied by adverse side effects<sup>12</sup> that may contribute to suboptimal adherence and/or treatment discontinuation or to emergent cardiometabolic comorbidities.<sup>13,14</sup> Despite a number of available antipsychotics, there remains a need for effective therapies with acceptable tolerability profiles that support long-term use.<sup>15-17</sup>

Based on data from clinical trials,<sup>18,19</sup> real-world settings,<sup>20-22</sup> meta-analyses,<sup>23,24</sup> and pooled analyses,<sup>25</sup> olanzapine is one of the most effective antipsychotics for the treatment of schizophrenia.<sup>26,27</sup> Olanzapine also effectively treats manic or mixed episodes associated with BD-I and reduces relapse risk during maintenance treatment.<sup>28-30</sup> While olanzapine's efficacy is well established,<sup>18,23,28,29,31</sup> the clinical utility of olanzapine has been hampered by the risk of substantial weight gain and metabolic effects,<sup>32-38</sup> such as elevations in blood glucose and lipid concentrations, waist circumference increases, and development of

metabolic syndrome.<sup>36,37,39</sup> Approximately 80% of patients gain at least 5 kg with long-term olanzapine treatment,<sup>40</sup> and this weight gain can continue over several months or even years.<sup>40-43</sup> In studies lasting at least 48 weeks, 64% of patients taking olanzapine gained at least 7% of their baseline body weight, and 12% gained at least 25% of their baseline body weight.<sup>40</sup> Increases in waist circumference, reflecting central fat accumulation, are associated with higher cardio-metabolic and mortality risks.<sup>44,45</sup> Consistent with weight gain and/or increases in waist circumference, long-term olanzapine use increases the risk of developing diabetes or hyperlipidemia,<sup>46-49</sup> as well as cardiovascular disease.<sup>45</sup>

The endogenous opioid receptor system is involved in the regulation of weight gain and metabolism.<sup>50-55</sup> Opioid receptors exist in both the central nervous system and in the periphery (eg, the pancreas, muscle, and liver),<sup>56-58</sup> making the opioid system a potential therapeutic target for addressing antipsychotic-associated weight gain. A combination of olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM; Lybalvi, Alkermes, Inc.) was recently approved by the US Food and Drug Administration (FDA) for the treatment of adults with schizophrenia or BD-I.<sup>59</sup> OLZ/SAM provides the antipsychotic efficacy of olanzapine, but with less weight gain.<sup>60-62</sup> OLZ/SAM is being developed to include 5-, 10-, 15-, or 20-mg doses of olanzapine (similar to dose ranges approved for adults with schizophrenia or BD-I)<sup>40</sup> with a fixed 10-mg dose of samidorphan in a single tablet.

## Overview of Clinical Trials

The effects of OLZ/SAM on weight gain and body composition have been previously characterized in preclinical studies in rats and nonhuman primates.<sup>63</sup> In this narrative review, we summarize the clinical data for OLZ/SAM and describe its overall efficacy and safety profile.

The clinical development program of OLZ/SAM includes 18 studies: 10 Phase 1,<sup>64-72</sup> two Phase 2,<sup>60,73</sup> three randomized, double-blind Phase 3 (Study A307; NCT03187769),<sup>61,62</sup> and three open-label, long-term, phase 3 safety extension studies (Study A308; NCT03201757)<sup>74,75</sup> (Supplemental Table 1). These studies provided information on the pharmacokinetics,<sup>64-69</sup> safety,<sup>70,74,75</sup> and efficacy (both antipsychotic efficacy as well as mitigation of weight gain relative to olanzapine [ie, weight efficacy])<sup>60-62</sup> of OLZ/SAM.

## Pharmacology and Mode of Action of Samidorphan

The body's endogenous opioid system is involved in the regulation of weight and metabolism.<sup>50–55</sup> Samidorphan is an opioid receptor antagonist that binds to and blocks opioid receptors.<sup>76,77</sup> The exact mechanism(s) by which samidorphan mitigates olanzapine-associated weight gain is unknown. Samidorphan has unique binding properties, functional activity, and pharmacokinetic attributes that differentiate it from other opioid antagonists.<sup>77–79</sup> It is thought that in the central nervous system, opioid receptor blockade may reduce the rewarding effects of stimuli in systems where aberrant opioid signaling may contribute to motivational dysregulation, such as in behavioral addiction (eg, binge-eating or gambling).<sup>80–82</sup> In the periphery, blockade or genetic ablation of opioid receptors alters fat accumulation and glucose utilization, as well as glucose homeostasis.<sup>63,83–85</sup> Therefore, the weight-mitigating properties of samidorphan in combination with olanzapine may be mediated through opioid receptor blockade in both central and peripheral compartments.

## Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of oral olanzapine and samidorphan have been extensively characterized alone and in combination.<sup>64–67,71,79,86,87</sup> Samidorphan has an oral bioavailability of 69% and a half-life of approximately 7 to 10 hours,<sup>79,87</sup> making it suitable for once-daily dosing in combination with olanzapine. Combining olanzapine with samidorphan did not affect the pharmacokinetics of either drug.<sup>66,71</sup> After once-daily dosing of OLZ/SAM at doses of 10/10 mg to 20/10 mg, steady-state olanzapine exposures increased dose proportionally.<sup>66</sup> In addition, consuming a high-fat, high-calorie meal prior to taking OLZ/SAM had no clinically relevant effects on the pharmacokinetics of olanzapine or samidorphan; therefore, OLZ/SAM can be taken with or without food.<sup>67</sup>

The olanzapine component of OLZ/SAM was bioequivalent to branded olanzapine oral tablets (Zyprexa, Eli Lilly and Company; [Supplemental Figure 1A](#)).<sup>64</sup> Furthermore, coadministration of OLZ/SAM with lithium or valproate had no clinically significant effect on systemic exposures of lithium or valproate ([Supplemental Figures 1B](#) and [C](#)).<sup>68</sup>

Drug-drug interactions known to be important for olanzapine should be considered important for OLZ/SAM as

well.<sup>40</sup> In addition, coadministration of OLZ/SAM with rifampin, a strong inducer of cytochrome P450 [CYP]3A4 and an inducer of uridine 5'-diphospho-glucuronosyltransferase [UGT] enzymes, decreased the total systemic exposure of olanzapine and samidorphan by 48% and 73%, respectively.<sup>65</sup> This effect is consistent with the known metabolic pathways for olanzapine (primarily via UGT-mediated direct glucuronidation and CYP-mediated oxidation)<sup>88,89</sup> and for samidorphan (predominately mediated by CYP3A4).<sup>79</sup> Therefore, concomitant use of OLZ/SAM with strong CYP3A4 inducers, such as rifampin, is not recommended.<sup>59</sup>

Subjects with severe renal impairment had up to a 2.3-fold increase in the total systemic exposure of olanzapine and samidorphan, while subjects with moderate hepatic impairment had up to 1.7-fold increases in total systemic exposure of olanzapine and samidorphan.<sup>69</sup> No dose adjustment is needed for OLZ/SAM in patients with hepatic or renal impairment, but OLZ/SAM is not recommended for patients with end-stage renal disease.<sup>59</sup>

Based on a thorough QT study conducted in patients with schizophrenia, OLZ/SAM, at doses up to a supratherapeutic dose of 30/30 mg, had no clinically relevant effect on electrocardiogram parameters, including QT interval.<sup>70</sup> Because no formal QT study had been conducted previously with olanzapine, this study fills an important information gap and provides further clinical context for the safety of OLZ/SAM treatment. [Supplemental Table 1](#) summarizes these data, as well as data from other pharmacokinetic and pharmacodynamic studies.

The abuse potential of samidorphan has been assessed<sup>90</sup> in a study with naltrexone, an opioid antagonist with no abuse potential,<sup>91</sup> serving as a negative control. Samidorphan's score on a drug-liking visual analog scale was similar to both placebo and naltrexone, indicating that samidorphan has no abuse potential.<sup>90</sup> Furthermore, at doses of 10 mg and 30 mg, samidorphan had significantly lower drug-liking scores compared with those of the positive controls, oxycontin and pentazocine, which are scheduled drugs with known abuse potential.

## Efficacy and Safety Overview

The antipsychotic efficacy of OLZ/SAM was primarily evaluated in a pivotal phase 3 study in patients with an acute exacerbation of schizophrenia,<sup>61</sup> while weight efficacy was primarily evaluated in a pivotal phase 3 study of stable

outpatients with schizophrenia.<sup>62</sup> Additional studies support the antipsychotic<sup>60,62</sup> and weight mitigation<sup>60</sup> efficacy of OLZ/SAM. The durability of antipsychotic and weight mitigation effects, as well as long-term effects on metabolic parameters, were derived from two 52-week, open-label, extension studies.<sup>74,75</sup> These findings are summarized below; additional detailed descriptions can be found in [Tables 1](#) and [2](#).

[Table 3](#) presents a summary of adverse events (AEs) and other key safety observations. In addition to collecting safety information from different populations of patients with schizophrenia (ie, acutely ill inpatients and stable outpatients), OLZ/SAM safety information was also derived from a study in patients with schizophrenia and comorbid alcohol use disorder.<sup>73</sup> In general, the AE profile for OLZ/SAM was similar to that of olanzapine, except for less weight gain. Because samidorphan is an opioid antagonist, concomitant use of opioids was exclusionary in the OLZ/SAM clinical trials, and OLZ/SAM is contraindicated in patients using opioids and in those undergoing acute opioid withdrawal.<sup>59</sup>

## Specific Study Results Related to Antipsychotic Effects

The phase 3 ENLIGHTEN-1 study evaluated the antipsychotic efficacy of OLZ/SAM in patients experiencing an acute exacerbation of schizophrenia requiring inpatient treatment. Treatment with OLZ/SAM resulted in significant improvements in symptoms compared with placebo at week 4, as measured by changes in Positive and Negative Syndrome Scale (PANSS) total scores from baseline<sup>61</sup> ([Figure 1A](#), [Table 2](#)). Improvement in PANSS scores with OLZ/SAM relative to placebo was similar to that observed with olanzapine; [Figure 1A](#), [Table 2](#)). Antipsychotic efficacy of OLZ/SAM relative to placebo was also supported by improvements in Clinical Global Impression-Severity (CGI-S) scores<sup>61</sup> ([Table 2](#)). The inclusion of samidorphan in OLZ/SAM did not negatively impact the antipsychotic efficacy of olanzapine.<sup>59</sup>

The efficacy of OLZ/SAM in controlling symptoms of schizophrenia was further supported by findings from ENLIGHTEN-2,<sup>62</sup> a pivotal study assessing weight gain as the primary endpoint. In that study, 24 weeks of treatment with either OLZ/SAM or olanzapine resulted in similar improvements in PANSS total and CGI-S scores ([Figure 1B](#); [Table 2](#)). Details and key findings on these and other studies assessing antipsychotic effects of OLZ/SAM are provided in [Table 2](#) and in [Figure 1B](#) and [C](#). The long-term effects of OLZ/SAM are summarized below.

## Specific Study Results Related to Effects on Weight, Waist Circumference, and Metabolic Parameters

The 24-week phase 3 ENLIGHTEN-2 study primarily assessed the weight profile of OLZ/SAM versus olanzapine in stable outpatients with schizophrenia ([Table 1](#)).<sup>62</sup> Patients treated with OLZ/SAM gained significantly less weight than those treated with olanzapine ([Table 2](#)).<sup>62</sup> [Figure 2A](#) depicts the mean percent body weight changes in this study, which were similar to the findings observed in a phase 2 dose-finding study ([Figure 2B](#)).<sup>60</sup> In the 24-week study, the least squares (LS) mean percent weight change from baseline to the end of treatment was 4.2% with OLZ/SAM versus 6.6% with olanzapine, yielding an LS mean difference of  $-2.4\%$ .<sup>62</sup> In the phase 2 study, the LS mean percent change from baseline in weight at week 12 was 2.6% with OLZ/SAM versus 4.1% with olanzapine, yielding an LS mean difference between groups of  $-1.5\%$ .<sup>60</sup> In both studies, patients treated with olanzapine and OLZ/SAM had similar weight gain for the first 4 to 6 weeks. With OLZ/SAM, weight gain stabilized thereafter, whereas patients who received olanzapine continued to gain weight throughout the remainder of the treatment period.<sup>60,62</sup> In ENLIGHTEN-2, this resulted in an alteration of the weight gain trajectory (eg, the distribution curve of weight gain was shifted for OLZ/SAM compared with olanzapine, indicating that fewer patients gained weight across a wide range of percent weight gain cutoffs; [Figure 2C](#)).

In addition to assessing differences in mean percent weight gain, the ENLIGHTEN-2 study assessed the proportion of patients gaining at least 10% of their body weight as a coprimary endpoint. The risk of gaining 10% or more of body weight from baseline was reduced by 50% with OLZ/SAM compared with olanzapine. In psychiatric practice, a weight gain of 7% or more is considered to be clinically significant.<sup>92,93</sup> As with the 10% weight gain threshold, the odds of gaining 7% body weight or more from baseline at week 24 was also reduced by 50% for OLZ/SAM compared with olanzapine ([Table 2](#); [Figure 2C](#)). Based on a number needed to treat (NNT) analysis of the proportion of patients with clinically significant weight gain at week 24, the NNT for OLZ/SAM versus olanzapine was 7 and 8 for the  $\geq 7\%$  and  $\geq 10\%$  weight gain thresholds, respectively ([Table 2](#)). Generally, NNTs less than 10 denote a clinically meaningful effect size, and the lower the NNT value, the better the treatment response.<sup>94,95</sup>



**Table 1** Summary of Study Design Features for Key Phase 2 and Phase 3 Studies

Parameter	Key Study					
	ENLIGHTEN-1 (ALK3831-A305) <sup>61</sup>	ENLIGHTEN-2 (ALK3831-A303) <sup>62</sup>	Dose-Finding Study (ALK3831-302) <sup>60</sup>	ENLIGHTEN-1-EXT (ALK3831-A306) <sup>74</sup>	ENLIGHTEN-2-EXT (ALK3831-A304) <sup>75</sup>	(ALK3831-401) <sup>73</sup>
Description	Phase 3 antipsychotic efficacy study	Phase 3 weight efficacy study	Phase 2 supportive efficacy and safety study	Phase 3 long-term safety and durability of treatment effect study	Phase 3 long-term safety and tolerability study	Phase 2 efficacy, safety, and tolerability study in other populations
Design	R, DB, C	R, DB, C	R, DB, C <sup>b</sup>	OL	OL	R, DB, C
Duration <sup>a</sup>	4 weeks	24 weeks	12 weeks	52 weeks	52 weeks	42–66 weeks
Year completed	2017	2018	2015	2018	2019	2017
Population	Adults with schizophrenia and an acute exacerbation of disease	Adults with schizophrenia	Adults with schizophrenia	Adults with schizophrenia	Adults with schizophrenia	Adults with schizophrenia and alcohol use disorder, with a recent exacerbation of disease
N	401	561	309	277	265	234
Interventions <sup>c</sup>	<ul style="list-style-type: none"> <li>● OLZ/SAM (10/10 mg or 20/10 mg)</li> <li>● Olanzapine (10 mg or 20 mg)</li> <li>● Placebo</li> </ul>	<ul style="list-style-type: none"> <li>● OLZ/SAM (10/10 mg or 20/10 mg)</li> <li>● Olanzapine (10 mg or 20 mg)</li> </ul>	<ul style="list-style-type: none"> <li>● Olanzapine<sup>d</sup> + placebo</li> <li>● Olanzapine<sup>d</sup> + samidorphan (5 mg)</li> <li>● Olanzapine<sup>d</sup> + samidorphan (10 mg)</li> <li>● Olanzapine<sup>d</sup> + samidorphan (20 mg)</li> </ul>	<ul style="list-style-type: none"> <li>● OLZ/SAM (10/10 mg, 15/10 mg, or 20/10 mg)</li> </ul>	<ul style="list-style-type: none"> <li>● OLZ/SAM<sup>e</sup></li> <li>● Olanzapine<sup>e</sup> + placebo</li> </ul>	

**Notes:** <sup>a</sup>Treatment period. <sup>b</sup>Olanzapine dosing was open label; the dose of coadministered samidorphan was blinded. <sup>c</sup>OLZ/SAM doses were given in the form XY, where X was the dose of olanzapine and Y was the dose of samidorphan. <sup>d</sup>Olanzapine was dosed per clinical judgment; the mean olanzapine dose/day across all treatment groups was 11–13 mg. <sup>e</sup>Doses of study drug were selected by investigators; the mean prescribed olanzapine dose/day was 14–15 mg; the samidorphan dose was 10 mg.

**Abbreviations:** EXT, extension; OL, open label; OLZ/SAM, combination of olanzapine and samidorphan; R, DB, C, randomized, double-blind, controlled (placebo and/or active comparator).

**Table 2** Summary of Study Findings from Key Phase 2 and Phase 3 Studies

Study	Key Findings
Antipsychotic efficacy study ENLIGHTEN-1 (ALK3831-A305) <sup>61</sup>	<ul style="list-style-type: none"> <li>• Treatment with OLZ/SAM resulted in significant improvement in PANSS total score (1° EP) at week 4 vs placebo (LS mean: -23.9 vs -17.5; <math>P &lt; 0.001</math>)</li> <li>• Magnitude of PANSS changes observed with OLZ/SAM was similar to that observed with olanzapine vs placebo at week 4 (LS mean: -22.8 vs -17.5, <math>P = 0.004</math>)</li> <li>• LS mean change in PANSS total score from baseline to week 4 was -6.4 (<math>P &lt; 0.001</math>) with OLZ/SAM and -5.3 (<math>P = 0.004</math>) with olanzapine</li> <li>• LS mean CGI-S scores (key 2° EP) at week 4 were -1.21, -1.27, and -0.84 in the OLZ/SAM, olanzapine, and placebo groups, respectively; OLZ/SAM and olanzapine had significant improvements vs placebo (<math>P = 0.002</math> and <math>P &lt; 0.001</math>, respectively)</li> <li>• Key safety findings are presented in Table 3</li> </ul>
Weight efficacy study ENLIGHTEN-2 (ALK3831-A303) <sup>62</sup>	<ul style="list-style-type: none"> <li>• Percent change in body weight from baseline to week 24 was 4.21% with OLZ/SAM and 6.59% with olanzapine, yielding an LS mean difference between OLZ/SAM and olanzapine of -2.38%; <math>P = 0.003</math> (co-1° EP)</li> <li>• Fewer patients gained <math>\geq 10\%</math> of their baseline body weight with OLZ/SAM vs olanzapine at week 24 (17.8% vs 29.8%, respectively), such that patients had half the risk of clinically significant weight gain with OLZ/SAM vs olanzapine (NNT<sup>3</sup>=8; odds ratio=0.50; <math>P = 0.003</math>; co-1° EP)</li> <li>• LS mean absolute change in body weight from baseline to week 24 was 3.18 kg with OLZ/SAM and 5.08 kg with olanzapine</li> <li>• Proportion of patients who gained <math>\geq 7\%</math> of their baseline weight was significantly lower for OLZ/SAM at week 24 than for olanzapine (27.5% vs 42.7%; NNT<sup>3</sup>=7; odds ratio=0.50; <math>P = 0.001</math>; 2° EP)</li> <li>• LS mean change from baseline to week 24 in waist circumference was 2.36 cm with OLZ/SAM and 4.47 cm with olanzapine (LS mean difference: -2.12 cm [95% CI: -3.35, -0.89])</li> <li>• Proportion of patients with a waist circumference increase of <math>\geq 5</math> cm from baseline was 26.8% and 43.2% in the OLZ/SAM and olanzapine groups, respectively (NNT<sup>3</sup>=6 [95% CI: 4, 13])</li> <li>• LS mean change from baseline to week 24 in PANSS total score was -8.2 with OLZ/SAM and -9.4 with olanzapine</li> <li>• Mean CGI-S scores at baseline were 3.7 and 3.5 in the olanzapine and OLZ/SAM groups, respectively; the LS mean change from baseline to week 24 was -0.5 and -0.4, respectively</li> <li>• Key safety findings are presented in Table 3</li> </ul>
Phase 2 supportive efficacy and safety study dose-finding study (ALK3831-302) <sup>60</sup>	<ul style="list-style-type: none"> <li>• PANSS score changes were similar between groups: LS mean (95% CI) change from baseline to week 12 in PANSS total score was -2.2 (-3.2, -1.3) with olanzapine + samidorphan and -2.9 (-4.5, -1.3) with olanzapine + placebo (1° EP)</li> <li>• Weight change with olanzapine + samidorphan was lower at week 12 than with olanzapine + placebo (mean absolute change was 1.9 kg vs 2.9 kg, respectively; LS mean difference: -1.0 [95% CI: -1.8, -0.2])</li> <li>• Key safety findings are presented in Table 3</li> </ul>
Long-term safety and durability of treatment effect study (I) ENLIGHTEN-1-EXT (ALK3831-A306) <sup>74</sup>	<ul style="list-style-type: none"> <li>• Assessment of safety and tolerability were primary study objectives</li> <li>• AEs occurred in 136 (49.1%) patients; most were mild or moderate in severity</li> <li>• The most common AEs were increased weight (13.4%), somnolence (8.3%), nasopharyngitis (4.0%), and headache (4.0%)</li> <li>• Mean change from baseline to week 52 in body weight was 1.86 kg</li> <li>• Parkinsonism, akathisia, and dyskinesia occurred in 7%, 5%, and 3% of patients, respectively</li> <li>• During the treatment and follow-up periods, 5 (1.8%) patients had suicidal ideation, suicidal behavior, or intentional overdose identified</li> <li>• Mean PANSS total score was 78.9 (n=248) at study start</li> <li>• Schizophrenia symptoms improved over 52 weeks of treatment, with PANSS total scores decreasing by 16.2 points at week 52</li> <li>• CGI-S scores also improved over the 52-week treatment period; mean CGI-S baseline score was 3.9 (n=248) and decreased by 0.9 points at week 52 (n=182 patients with available assessments)</li> </ul>

(Continued)

Table 2 (Continued).

Study	Key Findings
Long-term safety and durability of treatment effect study (2) ENLIGHTEN-2-EXT (ALK3831-A304) <sup>75</sup>	<ul style="list-style-type: none"> <li>• Assessment of safety and tolerability were primary study objectives</li> <li>• In total, 60.8% of patients experienced any AE; the majority were of mild or moderate severity</li> <li>• AEs occurring in ≥5% patients: weight decreased (8.7%), extra dose administered (7.9%), headache (6.8%), and weight increased (6.0%)</li> <li>• Mean change from baseline to week 52 in body weight was −0.03 kg</li> <li>• Mean change from baseline to week 52 in waist circumference was −0.35 cm</li> <li>• Rates of parkinsonism, akathisia, and dyskinesia were 4%, 2%, and 2%, respectively</li> <li>• 6.8% of patients experienced suicidal ideation and 0.4% experienced the suicidal behavior of preparatory acts or behavior</li> <li>• These outpatients had a mean baseline PANSS total score of 59.0 (n=265)</li> <li>• Mean PANSS total score remained stable (58.3 at week 52 in 168 patients with available assessments)</li> <li>• CGI-S scores changed little over the course of ENLIGHTEN-2-EXT (mean score at baseline: 3.1; mean score at week 52: 3.0)</li> </ul>
Other populations, treatment effects in schizophrenia and comorbid alcohol use disorder (ALK3831-401) <sup>73</sup>	<ul style="list-style-type: none"> <li>• The difference between OLZ/SAM and olanzapine on time to first event of exacerbation of disease symptoms was not significant (1° EP; hazard ratio: 0.91; 95% CI: 0.53, 1.56; P=0.746)</li> <li>• There were no between-group differences in alcohol use behavior, as measured by changes in WHO drinking risk level, number of heavy drinking days, or desire for alcohol</li> <li>• Similar improvements in PANSS total scores were observed with either treatment at week 63 relative to randomization (change of −5.4 for OLZ/SAM and of −3.4 for olanzapine)</li> <li>• Overall, 57.1% of patients treated with OLZ/SAM and 59.0% of patients treated with olanzapine reported any AEs</li> <li>• The most commonly reported AEs (occurring in ≥3% of patients in both groups) were weight gain, nasopharyngitis, and exacerbation of schizophrenia symptoms</li> <li>• Key safety findings are presented in Table 3</li> </ul>

**Notes:** <sup>a</sup>NNT values were calculated from the proportion of patients using a logistic regression model to adjust for covariates at baseline. Thus, the NNT and 95% CI values described here can differ from raw NNT estimates calculated from the actual rates without adjustment for covariates. In a study of human abuse potential, samidorphan had no abuse potential and had a profile consistent with naltrexone, a negative control in the study.<sup>90</sup>

**Abbreviations:** 1° EP, prespecified primary endpoint; 2° EP, prespecified secondary endpoint; AE, adverse event; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; EXT, extension; LS, least squares; NNT, number needed to treat; OLZ/SAM, combination of olanzapine and samidorphan; PANSS, Positive and Negative Syndrome Scale; WHO, World Health Organization.

OLZ/SAM was also associated with smaller increases in waist circumference compared with olanzapine (Table 2; Figure 3A),<sup>62</sup> which occurred as early as week 1. As with the distribution curve for weight gain, the distribution curve for waist circumference increases was also shifted. Fewer patients had waist circumference increases across a range of cutoff values in comparison to olanzapine. The risk of experiencing a 5-cm increase in waist circumference was 50% lower for patients treated with OLZ/SAM versus olanzapine (Table 2; Figure 3B). This is clinically significant, as a 5-cm or greater increase in waist circumference is associated with an increased risk of all-cause mortality and cardiovascular disease.<sup>44</sup> The NNT for the proportion of patients with a waist circumference increase of ≥5 cm in the OLZ/SAM group versus the olanzapine group was 6 (Table 2).

Changes in metabolic laboratory parameters in patients treated with olanzapine or OLZ/SAM in ENLIGHTEN-2 were generally small and were similar between groups (Figure 4A and B). In addition, there were little differences between the two treatment groups in metabolic parameter changes considered to be of potential clinical significance, based on commonly used thresholds (Supplemental Table 2). In the context of metabolic laboratory parameters, sustained shifts are more clinically relevant than single excursions resulting from visit-to-visit variability or inconsistencies in fasting status. Across the fasting lipid and glycemic parameters, the incidence of sustained shifts was substantially lower than the incidence of anytime shifts and was similar for both groups (Supplemental Table 2).

**Table 3** Summary of Adverse Events and Other Safety Measures During Double-Blind Treatment Periods of Completed Phase 2 and 3 Studies<sup>a</sup>

Parameter	Phase 2 ALK3831-302 Study (12 Weeks; Outpatients with Schizophrenia) (N=309)		Phase 2 ALK3831-401 Study (Up to 60 Weeks; Patients with Schizophrenia and Comorbid Alcohol Use Disorder) (N=229)		Phase 3 ENLIGHTEN-1 Study (4 Weeks; Patients with an Acute Exacerbation of Schizophrenia) (N=401)			Phase 3 ENLIGHTEN-2 Study (24 Weeks; Outpatients with Schizophrenia) (N=550)	
	Olanzapine (n=75)	OLZ/SAM <sup>b</sup> (n=234)	Olanzapine (n=117)	OLZ/SAM <sup>b</sup> (n=112)	Placebo (n=134)	Olanzapine (n=133)	OLZ/SAM <sup>b</sup> (n=134)	Olanzapine (n=276)	OLZ/SAM <sup>b</sup> (n=274)
Death, n (%) <sup>c</sup>	0	0	1 (0.9)	1 (0.9)	0	1 (0.8)	0	0	0
SAE, n (%)	2 (2.7)	11 (4.7)	12 (10.3)	7 (6.3)	0	1 (0.8)	1 (0.7)	7 (2.5)	10 (3.6)
AE leading to discontinuation, n (%)	3 (4.0)	21 (9.0)	13 (11.1)	10 (8.9)	7 (5.2)	3 (2.3)	2 (1.5)	27 (9.8)	33 (12.0)
Any AE, n (%)	41 (54.7)	127 (54.3)	69 (59.0)	64 (57.1)	60 (44.8)	73 (54.9)	73 (54.5)	227 (82.2)	203 (74.1)
AEs occurring in >5% of patients, n (%)									
Anxiety	1 (1.3)	3 (1.3)	3 (2.6)	2 (1.8)	8 (6.0)	7 (5.3)	8 (6.0)	9 (3.3)	1 (0.4)
Dry mouth	4 (5.3)	13 (5.6)	1 (0.9)	3 (2.7)	1 (0.7)	7 (5.3)	10 (7.5)	22 (8.0)	35 (12.8)
Extra dose administered <sup>d</sup>	0	0	0	0	0	0	0	17 (6.2)	14 (5.1)
Headache	4 (5.3)	5 (2.1)	4 (3.4)	2 (1.8)	4 (3.0)	7 (5.3)	8 (6.0)	11 (4.0)	11 (4.0)
Increased alanine aminotransferase	1 (1.3)	3 (1.3)	0	6 (5.4)	0	5 (3.8)	2 (1.5)	8 (2.9)	8 (2.9)
Increased appetite	6 (8.0)	16 (6.8)	0	0	0	1 (0.8)	1 (0.7)	34 (12.3)	30 (10.9)
Increased blood creatine phosphokinase	0	0	1 (0.9)	2 (1.8)	0	0	0	12 (4.3)	14 (5.1)
Increased waist circumference	0	0	0	0	0	0	0	22 (8.0)	17 (6.2)
Increased weight <sup>e</sup>	9 (12.0)	21 (9.0)	14 (12.0)	16 (14.3)	4 (3.0)	19 (14.3)	25 (18.7)	100 (36.2)	68 (24.8)
Insomnia	4 (5.3)	5 (2.1)	3 (2.6)	4 (3.6)	2 (1.5)	4 (3.0)	1 (0.7)	10 (3.6)	3 (1.1)
Nasopharyngitis	2 (2.7)	2 (0.9)	5 (4.3)	7 (6.3)	3 (2.2)	0	2 (1.5)	7 (2.5)	2 (0.7)
Nausea	4 (5.3)	14 (6.0)	0	1 (0.9)	3 (2.2)	1 (0.8)	0	8 (2.9)	7 (2.6)
Schizophrenia	1 (1.3)	7 (3.0)	6 (5.1)	5 (4.5)	8 (6.0)	2 (1.5)	1 (0.7)	4 (1.4)	2 (0.7)
Sedation	3 (4.0)	12 (5.1)	1 (0.9)	1 (0.9)	0	1 (0.8)	3 (2.2)	12 (4.3)	11 (4.0)
Somnolence	3 (4.0)	29 (12.4)	3 (2.6)	2 (1.8)	3 (2.2)	13 (9.8)	12 (9.0)	50 (18.1)	58 (21.2)
<b>Other Safety Measures, n (%)</b>									
Akathisia <sup>f</sup>	NA	NA	5 (4.3)	8 (7.1)	11 (8.2)	6 (4.5)	8 (6.0)	8 (2.9)	6 (2.2)
Dyskinesia <sup>f</sup>	NA	NA	3 (2.6)	6 (5.4)	2 (1.5)	1 (0.8)	2 (1.5)	2 (0.7)	4 (1.5)
Parkinsonism <sup>f</sup>	NA	NA	6 (5.1)	5 (4.5)	14 (10.4)	6 (4.5)	5 (3.7)	5 (1.8)	10 (3.6)
Suicidal ideation <sup>g</sup>	1 (1.3)	7 (3.0)	10 (8.5)	9 (8.0)	3 (2.2)	2 (1.5)	0	27 (9.8)	15 (5.5)
Suicidal behavior <sup>g</sup>	0	1 (0.4)	0	2 (1.8)	0	0	0	1 (0.4)	0

**Notes:** <sup>a</sup>All randomized patients who received ≥1 dose of study drug. <sup>b</sup>The dose of olanzapine was dosed at the discretion of the investigator in ALK3831-302 and ALK3831-401, and was given at doses of either 10 or 20 mg in ENLIGHTEN-1 and ENLIGHTEN-2. The dose of samidorphan was fixed at 10 mg, except for in the ALK3831-302 study, where samidorphan doses ranged from 5 to 20 mg. <sup>c</sup>The 2 deaths in study ALK3831-401 were due to chronic obstructive pulmonary disease (patient had received OLZ/SAM) and alcohol poisoning (patient had received olanzapine). The 1 death in ENLIGHTEN-1 was due to heroin intoxication after treatment ended (patient had received olanzapine). None of these deaths were considered related to treatment by investigators. <sup>d</sup>In phase 3 studies, sites were requested to report any extra dose of study drug administered as an AE (extra dose administered). These extra doses were accidentally taken by patients and were recorded for drug accountability reasons. <sup>e</sup>AEs of weight increased were based on reports/observations by the patient and/or investigator and are in contrast to weight changes, which were based on actual weight assessments. <sup>f</sup>Akathisia based on Barnes Akathisia Rating Scale global score ≥2; dyskinesia based on Abnormal Involuntary Movement Scale score of ≥3 on any of the first 7 items or a score of ≥2 on 2 or more of the first 7 items; parkinsonism based on Simpson-Angus Scale score of >3. <sup>g</sup>Suicidal ideation and suicidal behavior were based on the Columbia Suicide Severity Rating Scale. In study ALK3831-401, Columbia Suicide Severity Rating Scale values were reported during the double-blind treatment period and safety follow-up period combined.

**Abbreviations:** AE, adverse event; NA, not assessed; OLZ/SAM, combination of olanzapine and samidorphan; SAE, serious adverse event.



## Adverse Events in Phase 3 Efficacy Trials

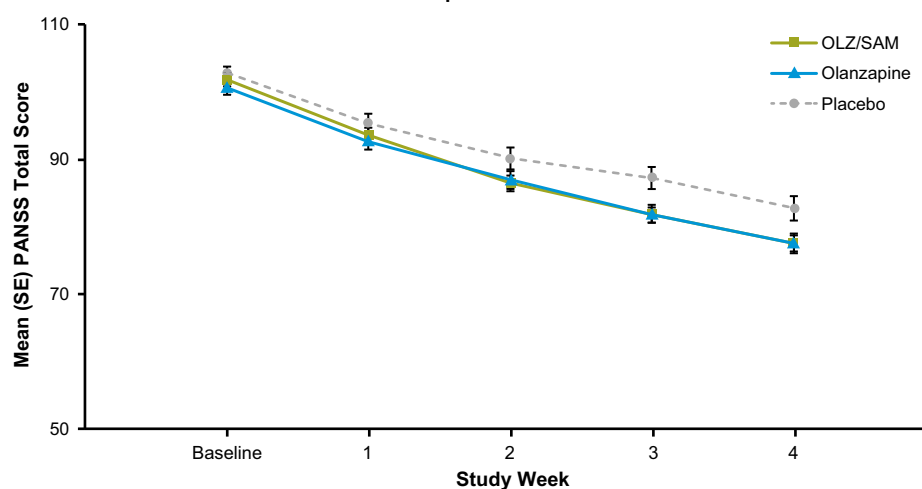
The AE profile of OLZ/SAM was consistent with the known AE profile of olanzapine. In ENLIGHTEN 1, adverse events that occurred at least twice the rate of placebo with OLZ/SAM included increased weight, somnolence, dry mouth, and headache; these were similar in type and frequency to those reported in the olanzapine group (Table 3).<sup>61</sup> In ENLIGHTEN-2, the most commonly reported AEs (in  $\geq 10\%$  of patients) associated with treatment were increased weight, somnolence, dry mouth, and increased appetite (Table 3).<sup>62</sup> In both studies, rates of serious AEs and AEs leading to discontinuation were low and were similar between groups (Table 3).

## Long-Term Treatment Effects

The long-term effects of OLZ/SAM on safety, tolerability, and symptoms of schizophrenia were investigated in two open-label, phase 3, 52-week extension studies, ENLIGHTEN-1-EXT and ENLIGHTEN-2-EXT<sup>74,75</sup> that enrolled patients who completed the respective antecedent phase 3 studies.<sup>61,62</sup>

Long-term tolerability was evidenced by low rates of AEs that led to treatment discontinuation: in both extension studies, the rate of discontinuation due to an AE was  $\leq 6\%$ .<sup>74,75</sup> Additionally, neither extension study reported any clinically meaningful changes over time in hematology, biochemistry, vital signs, or electrocardiogram parameters. The incidence of extrapyramidal symptoms and

### A Patients With an Acute Exacerbation of Schizophrenia



### B Patients With Stable Schizophrenia

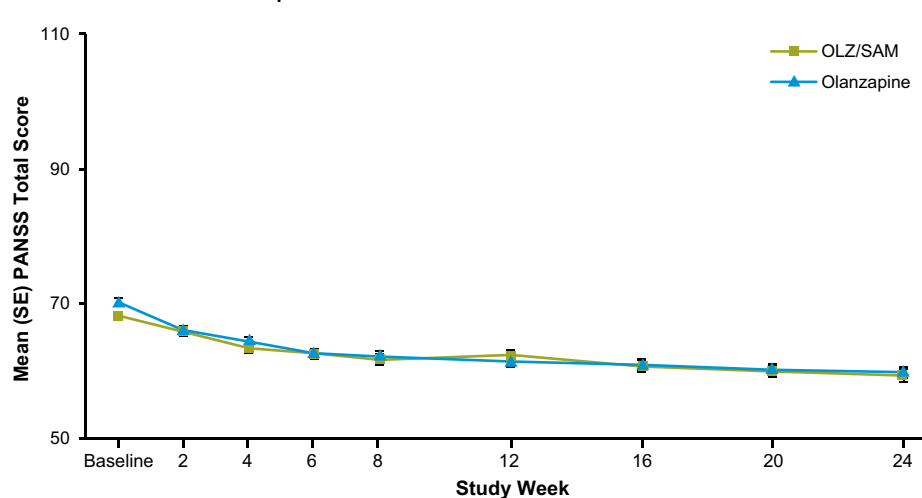
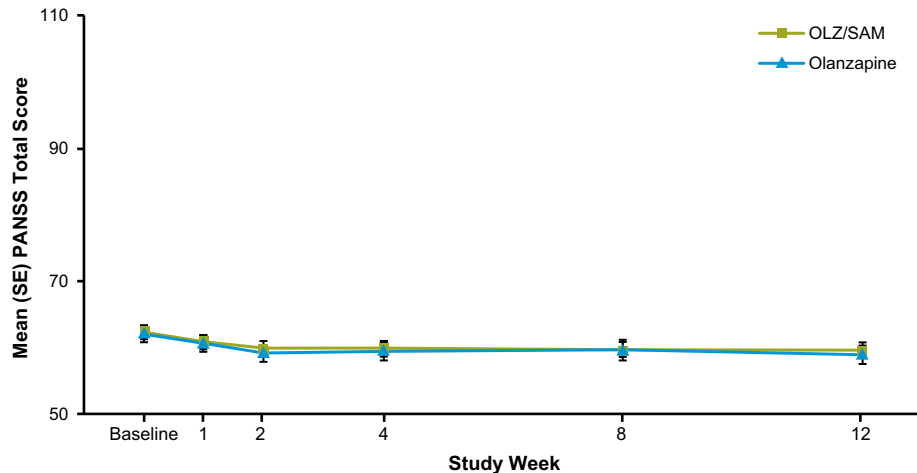
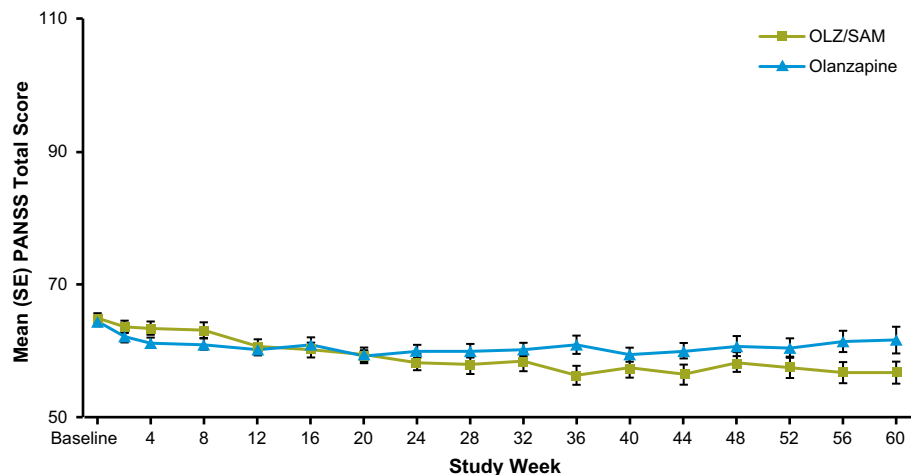


Figure 1 Continued.

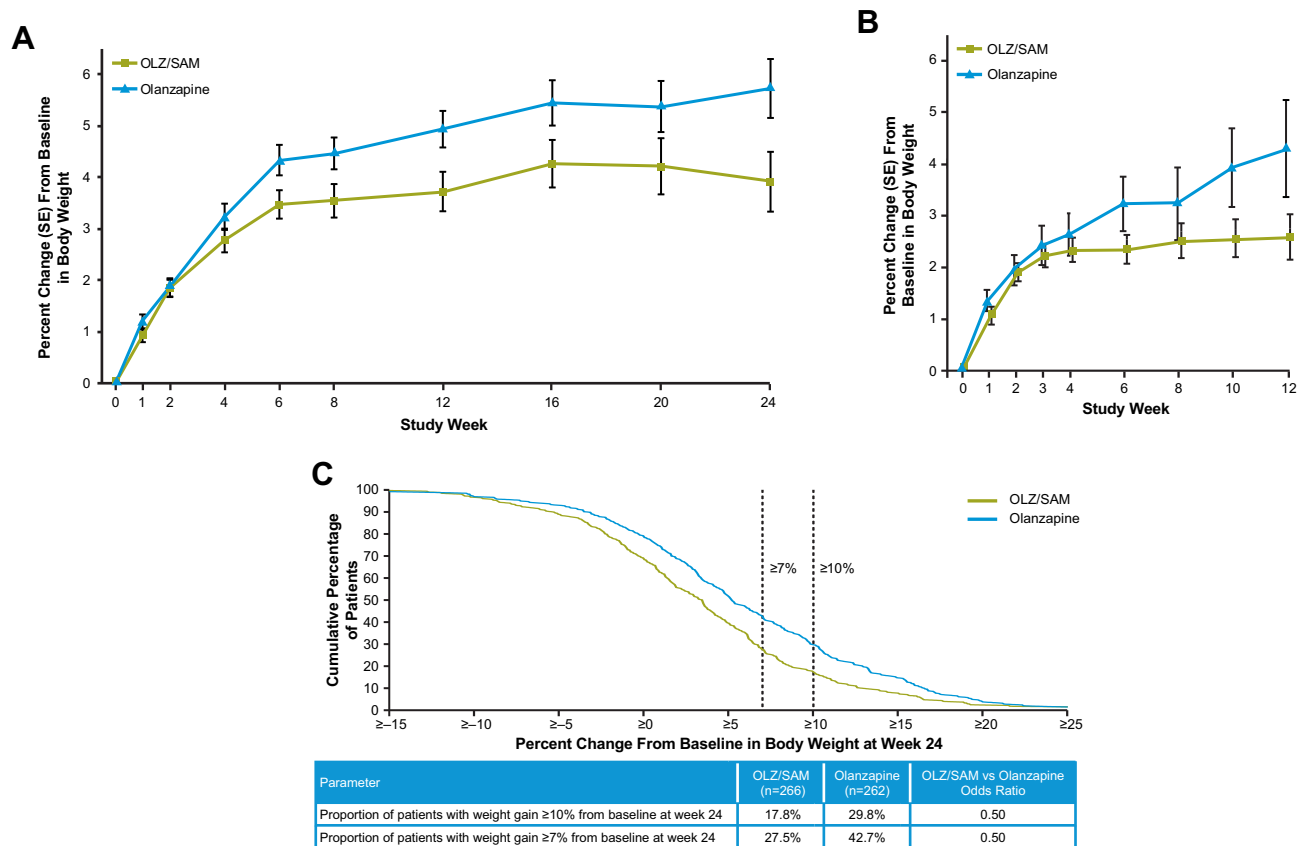
**C Patients With Stable Schizophrenia (Phase 2)****D Patients With Schizophrenia and Comorbid Alcohol Use Disorder (Phase 2)**

**Figure 1** Antipsychotic effects of OLZ/SAM and olanzapine in key phase 2 and 3 studies. Graphs depict absolute changes in PANSS total scores over time by treatment group in the randomized, controlled (active or placebo), double-blind ENLIGHTEN-1 (A), ENLIGHTEN-2 (B), ALK3831-302 (C), and ALK3831-401 (D) studies.<sup>60–62,73</sup> Panel (A) In the phase 3 ENLIGHTEN-1 study, antipsychotic efficacy, as measured by the change from baseline in the PANSS total score at week 4, was the primary endpoint. The baseline characteristics of treatment groups in ENLIGHTEN-1 were balanced. Panel (B) In the phase 2 ENLIGHTEN-2 study, antipsychotic efficacy, as measured by the change from baseline in the PANSS total score at week 24, was an “other” endpoint. The baseline characteristics of treatment groups in ENLIGHTEN-2 were balanced. Panel (C) In ALK3831-302, antipsychotic efficacy, as measured by the change from baseline in the PANSS total score at week 12 in the combined OLZ/SAM groups (OLZ/SAM 5/10 mg, 10/10 mg, and 20/10 mg) versus olanzapine was the primary endpoint; only the olanzapine + placebo and olanzapine + samidorphan 10-mg groups are presented here to allow cross-study comparisons. Panel (D) In ALK3831-401, antipsychotic efficacy, as measured by the change from baseline in the PANSS total score, was an “other” efficacy endpoint. Graph depicts observed changes with an MMRM approach. **Abbreviations:** OLZ/SAM, combination of olanzapine and samidorphan; MMRM, mixed-model repeated measures; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

suicidality was low in both long-term extension studies (Table 3).

Importantly, OLZ/SAM was effective in controlling symptoms of schizophrenia over 52 weeks of treatment (Table 2; Figure 5A and B), as evidenced by sustained improvements in PANSS and CGI-S scores over time. However, in contrast to what has been described with long-term olanzapine treatment, weight remained stable during open-label OLZ/SAM treatment in both long-

term extension studies (Figure 5C and D).<sup>74,75</sup> The observed long-term changes in weight were consistent with weight changes observed with other second-generation antipsychotics, although comparisons to other antipsychotics must be interpreted cautiously owing to different study objectives, designs, and analyses, and to the lack of comparators in these studies.<sup>96–99</sup> Waist circumference also remained stable during long-term OLZ/SAM treatment.<sup>75</sup>



**Figure 2** Weight effects of patients treated with OLZ/SAM and olanzapine: the mean (SE) percent change in weight from baseline for ENLIGHTEN-2 (A) and for ALK3831-302 (B), and the cumulative frequency distribution of percent change from baseline in body weight at week 24 (C). In ENLIGHTEN-2, the baseline characteristics of treatment groups in ENLIGHTEN-2 were balanced. Panel (C) depicts how OLZ/SAM reduced the risk of weight gain relative to olanzapine across a wide range of cutoffs; this plot presents the range of weight changes at week 24 on the x axis (ranging from a weight loss of 15% weight loss [ $-15\%$ ] to a weight gain of 25%) versus the proportion of patients gaining this amount of weight or more on the y axis. The curve for OLZ/SAM generally falls below the curve for olanzapine, indicating that a smaller proportion of patients treated with OLZ/SAM experienced weight gain across the majority of cutoffs, including gaining any weight ( $\geq 0\%$ ) or at more substantial levels of weight gain (eg,  $\geq 7\%$  and  $10\%$  cutoffs [marked in the figure by vertical dotted lines]). Observed data are depicted in panels (A (MMRM approach) and B). Panel (C) reprinted with permission from the *American Journal of Psychiatry* (Copyright ©2020). American Psychiatric Association. All Rights Reserved.<sup>62</sup>

**Abbreviations:** MMRM, mixed-model repeated measures; OLZ/SAM, combination of olanzapine and samidorphan; SE, standard error.

In general, long-term changes in metabolic laboratory parameter values were small and remained stable (Supplemental Table 3).<sup>74,75</sup> In addition, there was little change in glycosylated hemoglobin (hemoglobin A1c) values, suggesting that glycemic control was maintained with long-term OLZ/SAM treatment.<sup>74,75</sup>

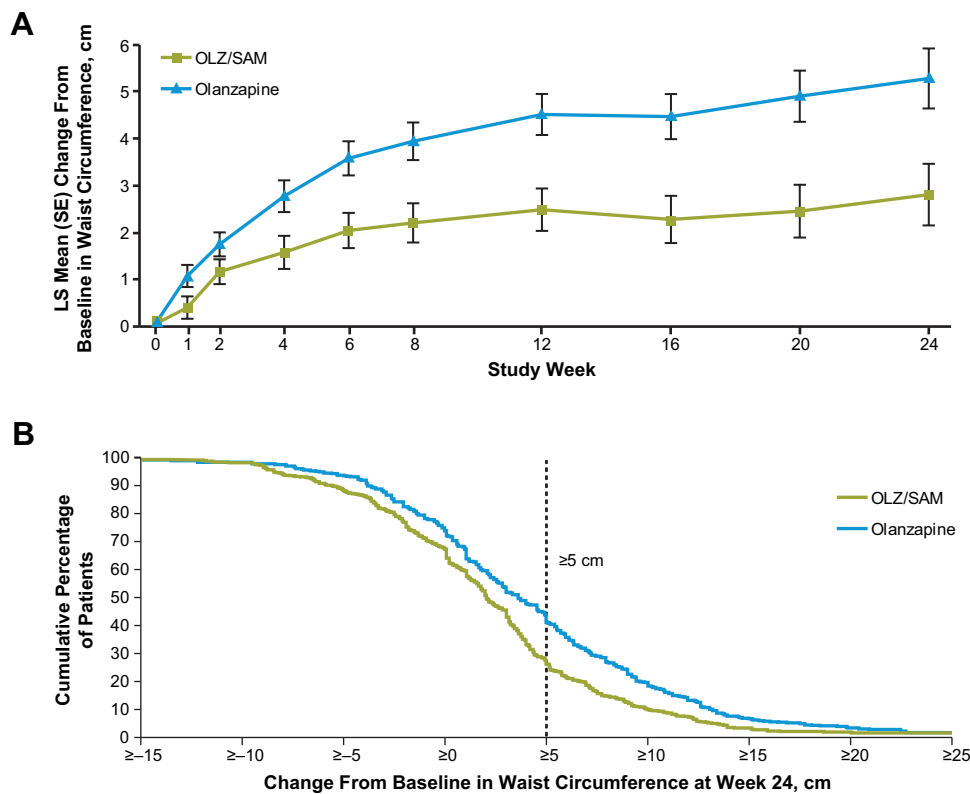
Results from numerous long-term treatment studies have indicated that patients discontinue olanzapine less frequently, or take longer to do so, compared with most other antipsychotics, and this is attributed to its efficacy in treating and controlling symptoms.<sup>18–20</sup> In the OLZ/SAM extension studies, the effectiveness of OLZ/SAM in controlling symptoms of schizophrenia was supported by the low rates of all-cause discontinuation, with nearly two thirds of patients (66.1% in ENLIGHTEN-1-EXT; 63.0% in ENLIGHTEN-2-EXT) completing the respective treatment periods.<sup>74,75</sup> This completion rate is higher than what is typically observed in

similar 1-year extension studies with other antipsychotics (ie, brexpiprazole, cariprazine, and lurasidone), which average less than a 50% completion rate.<sup>96–100</sup> Time to all-cause discontinuation is presented graphically for each extension study in Figure 5E and F.

Results from the long-term extension studies should be considered in light of some limitations: (1) these were single-arm, open-label studies (ie, randomization was lost at study entry) without comparators, (2) the interpretation of long-term data may be impacted by missing data due to patient discontinuations over the long study duration, and (3) the studies may have selected for patients who responded favorably to OLZ/SAM treatment in the preceding studies.

## Other Populations

The efficacy, safety, and tolerability of OLZ/SAM compared with olanzapine have also been examined in patients with



**Figure 3** Effects on waist circumference profiles in patients treated with OLZ/SAM and olanzapine in ENLIGHTEN-2. **(A)** LS mean change from baseline in waist circumference and **(B)** cumulative frequency distribution of percent change from baseline in waist circumference at week 24. The waist circumference analysis presented in Panel **(A)** is based on an ANCOVA model with a multiple imputation approach for missing postbaseline assessments.<sup>62</sup> Panel **(A)** reprinted with permission from the *American Journal of Psychiatry* (Copyright ©2020), American Psychiatric Association. All Rights Reserved.<sup>62</sup>

**Abbreviations:** ANCOVA, analysis of covariance; LS, least squares; OLZ/SAM, combination of olanzapine and samidorphan; SE, standard error.

schizophrenia and comorbid alcohol use disorder.<sup>73,101</sup> In this study, while treatment with OLZ/SAM or olanzapine resulted in similar times to a composite endpoint of worsening illness and there was no added benefit of OLZ/SAM compared with olanzapine with regard to drinking behaviors, patients in both treatment groups had reduced alcohol use and improved psychiatric symptoms. Overall, OLZ/SAM treatment for up to 9 months was generally well tolerated in this patient population (safety data are summarized in Table 3). In addition, treatment with OLZ/SAM resulted in similar effectiveness to olanzapine in controlling symptoms of schizophrenia, based on changes in PANSS total scores over 60 weeks (Figure 1D).<sup>73</sup>

## Evidence for the Use of OLZ/SAM in Bipolar I Disorder

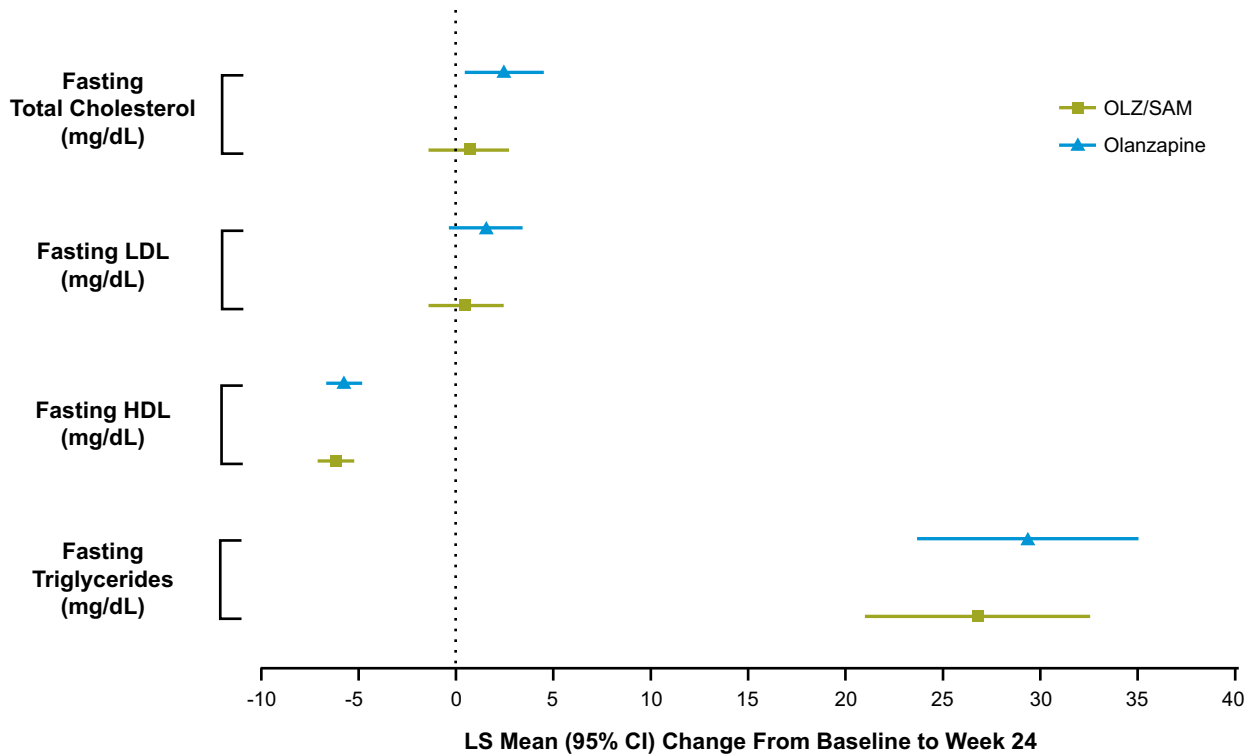
OLZ/SAM is approved in the United States for treatment of manic or mixed episodes in BD-I, as monotherapy or as an adjunct to lithium or valproate, as well as for maintenance monotherapy in BD-I. The efficacy of OLZ/SAM in the treatment of adult patients with BD-I has been

established based on adequate and well-controlled studies of orally administered olanzapine.<sup>40</sup> Additionally, the olanzapine component of OLZ/SAM was shown to be bioequivalent to olanzapine in the branded product, Zyprexa.<sup>64</sup> Furthermore, treatment with OLZ/SAM had no clinically significant effect on lithium or valproate pharmacokinetics.<sup>68</sup> In schizophrenia patients, samidorphan did not negatively affect the efficacy of olanzapine when administered as OLZ/SAM.<sup>59</sup> Finally, OLZ/SAM consistently mitigated olanzapine-associated weight gain across a range of species/populations (eg, rodents, non-human primates, healthy individuals, and patients with schizophrenia),<sup>60,62,71</sup> and antipsychotic-associated weight gain and metabolic dysregulation occur independently of disease.<sup>102–104</sup>

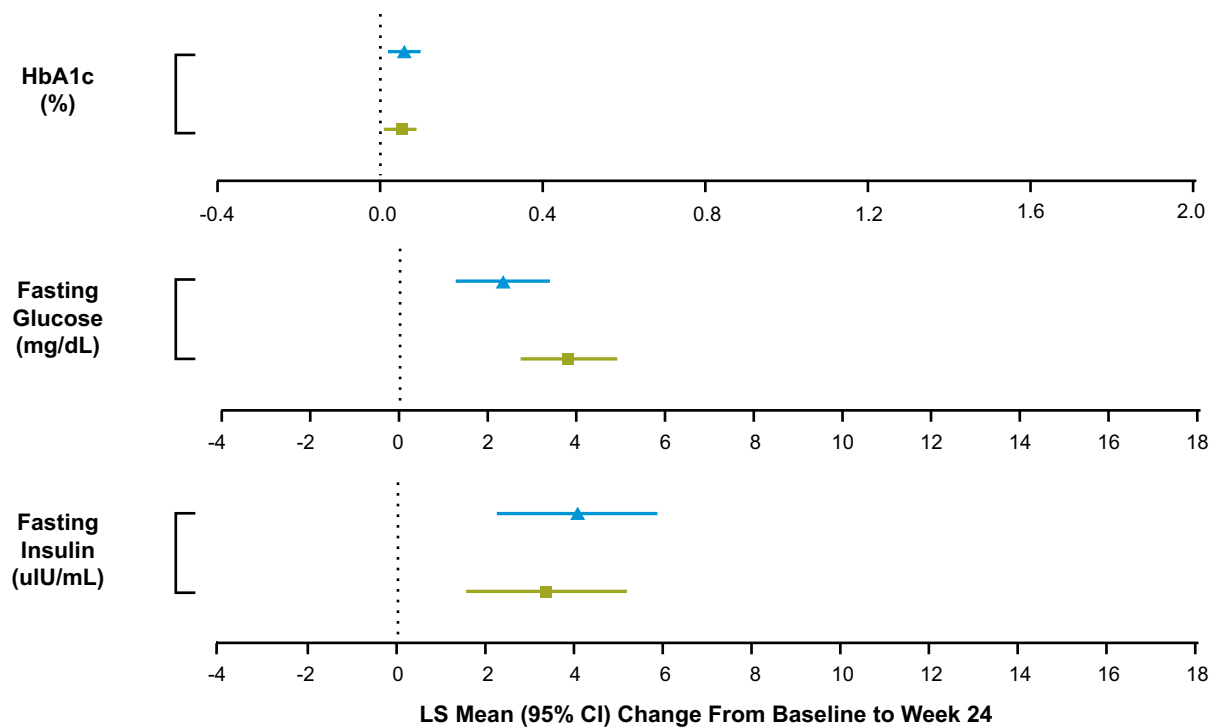
## Clinical Perspectives

Most second-generation antipsychotics used in the context of serious mental illness are associated with weight gain,<sup>14</sup> which may lead to detrimental effects in patients, including lower self-esteem and the potential for negative

**A**



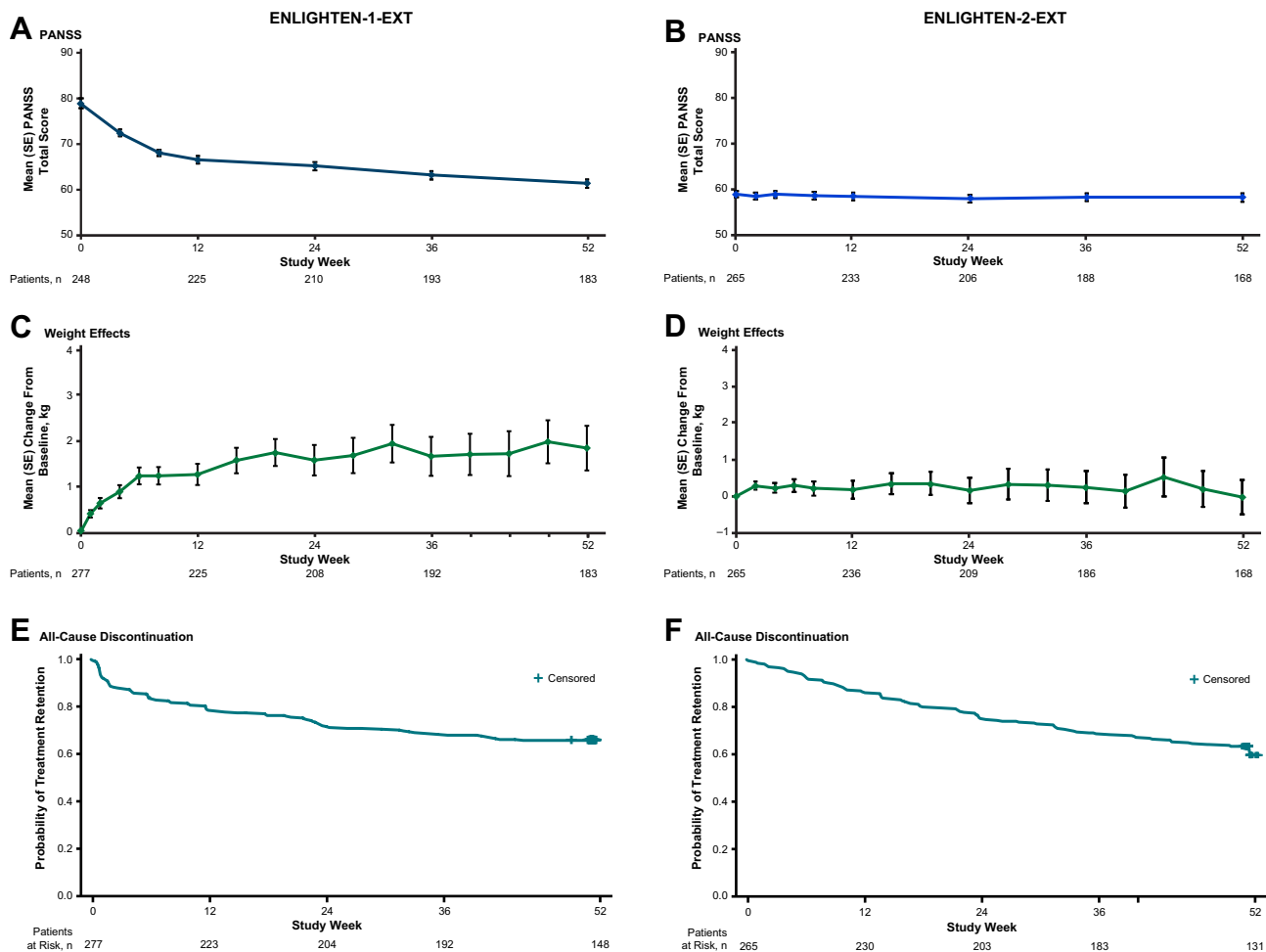
**B**



**Figure 4** ENLIGHTEN-2 metabolic laboratory parameters: LS mean (95% CI) changes from baseline to week 24 for **(A)** fasting lipids and **(B)** HbA1c, fasting glucose, and fasting insulin. Values are based on a mixed model with repeated measures using observed data.

**Abbreviations:** CI, confidence interval; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; OLZ/SAM, combination of olanzapine and samidorphan.





**Figure 5** Antipsychotic effects, weight effects, and time to all-cause discontinuation in ENLIGHTEN-1-EXT<sup>74</sup> (A, C, E) and ENLIGHTEN-2-EXT<sup>75</sup> (B, D, F), respectively. Data presented above are in all patients; in both studies, all patients received OLZ/SAM treatment. Prior to entering ENLIGHTEN-1-EXT, patients participated in the 4-week ENLIGHTEN-1 study, where entry criteria specified that patients had to be experiencing an acute exacerbation of schizophrenia. Prior to entering ENLIGHTEN-2-EXT, patients participated in the 24-week ENLIGHTEN-2 study, where entry criteria specified that patients with schizophrenia be stable outpatients. In all panels, baseline/week 0 refers to extension study start. Panels (B, D, and F) are reprinted with permission from *Schizophrenia Research* (Copyright ©2021).<sup>75</sup>  
**Abbreviations:** EXT, extension; OLZ/SAM, combination of olanzapine and samidorphan; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

outcomes when patients do not fill prescriptions or take their medication.<sup>105–108</sup> Additionally, excess weight gain may exacerbate cardiometabolic risk factors,<sup>45,109</sup> especially in people with serious mental illness, including those with schizophrenia or BD-I.<sup>110,111</sup> This is partially attributable to the rising prevalence of obesity in the general population, and in patients with schizophrenia and BD-I in particular.<sup>112–114</sup> Additionally, patients with serious mental illness have an increased prevalence of risk factors for cardiovascular disease relative to the general population, which contributes to excess early mortality in these patients.<sup>115–117</sup>

Up until now, there have not been any FDA-approved agents that address the specific issue of antipsychotic-induced weight gain. Several potential strategies have

been investigated to reduce or mitigate antipsychotic-associated weight gain, including both nonpharmacologic and pharmacologic interventions. With some exceptions, studies of pharmacologic options have mostly assessed weight reduction in patients who have already experienced antipsychotic-associated weight gain, rather than investigating the prevention of antipsychotic-associated weight gain from the outset.<sup>118</sup>

An example of an “off-label” pharmacologic intervention that has been extensively studied is adjunctive metformin. In a meta-analysis of 32 randomized studies evaluating 15 pharmacologic agents for minimizing or attenuating antipsychotic-associated weight gain, metformin outperformed other agents versus placebo.<sup>119</sup> In the 7 trials (lasting 6 to 16 weeks) informing that analysis, metformin treatment was associated with a weight loss of  $-2.94$  kg versus placebo in patients who

had already experienced antipsychotic-associated weight gain.<sup>119</sup> However, this meta-analysis did not detect a weight change difference versus placebo when metformin was initiated concomitantly with antipsychotics.<sup>119</sup> In an updated systematic review and meta-analysis on this topic that included 10 metformin studies,<sup>118</sup> a mean 3.17-kg reduction in weight versus placebo was observed across studies. However, 3 of the 4 studies that investigated the prevention of antipsychotic-associated weight gain with metformin were negative,<sup>120–122</sup> while one was positive in patients who completed the study.<sup>123</sup>

For other pharmacologic interventions that have been assessed for minimizing antipsychotic-associated weight, there is inadequate evidence of effect, no clinical benefit, or an AE profile that offsets any potential benefits for reducing existing antipsychotic-associated weight gain.<sup>124</sup> Current guidelines suggest that the use of such agents should be considered in the context of limited long-term data and the potential for AEs.<sup>11</sup> Because OLZ/SAM is a single tablet, concerns regarding adding medications onto an existing regimen to reduce weight (eg, AEs, drug-drug interaction effects, and pill burden) may be avoided.

Appropriate antipsychotic selection for an individual patient requires that clinicians consider the benefits and risks of the treatment, as well as bearing in mind an individual patient's characteristics and treatment goals. For patients who may benefit from the established efficacy of olanzapine, clinicians have to balance choosing this highly effective therapy for their patient while risking other safety concerns, including the risk of significant weight gain and its associated long-term health consequences.<sup>32,33</sup> OLZ/SAM may be an option in this regard, as it provides similar efficacy compared with olanzapine but with significantly less weight gain. The weight-mitigating effects of OLZ/SAM relative to olanzapine have been replicated in at least 2 studies and is supported by long-term data extending over 1 year.<sup>41,125,126</sup> For certain patients who are at greater risk of antipsychotic-associated weight gain, including those with a lower body mass index<sup>41,125,126</sup> and those with less prior exposure to antipsychotics (eg, patients early in illness), OLZ/SAM may also be useful.<sup>127,128</sup> However, it should be noted that, because OLZ/SAM contains the opioid antagonist samidorphan, it should not be used in patients using opioids or in those undergoing acute opioid withdrawal.<sup>59</sup>

One ongoing OLZ/SAM study will provide additional long-term safety and tolerability data (NCT03201757). Another ongoing study (NCT03187769; ENLIGHTEN-

Early) is assessing treatment effects of OLZ/SAM in patients early in their disease course with schizophrenia, schizophreniform disorder, or BD-I.

## Conclusions

OLZ/SAM provides the established efficacy of olanzapine while mitigating olanzapine-associated weight gain through opioid receptor blockade. Studies to date have characterized the pharmacokinetics, safety, and efficacy (both antipsychotic and weight efficacy) of OLZ/SAM. Clinical pharmacokinetic data indicate the feasibility of once-daily dosing with OLZ/SAM and provide support for the use of OLZ/SAM in BD-I based on bioequivalence of OLZ/SAM to olanzapine and the lack of clinically significant effects of adjunctive OLZ/SAM on lithium or valproate pharmacokinetics. The antipsychotic and weight gain mitigation efficacy of OLZ/SAM was observed in multiple studies; these effects were durable and were maintained during open-label treatment. Overall, data from more than 1600 patients in studies of differing designs, durations, and treatment populations indicate an AE profile for OLZ/SAM that is similar to that of olanzapine, with the exception of less weight gain. Taken together, these data support the recent approval of OLZ/SAM as a clinically useful option for patients with schizophrenia or BD-I and its suitability for long-term treatment.

## Abbreviations

1° EP, prespecified primary endpoint; 2° EP, prespecified secondary endpoint; AE, adverse event; ANCOVA, analysis of covariance;  $AUC_{\infty}$ , area under the plasma concentration-time curve from time 0 to infinity; BD-I, bipolar I disorder; CGI-S, Clinical Global Impression-Severity;  $C_{max}$ , maximum plasma concentration; CYP, cytochrome P450 enzyme; ENLIGHTEN-1-EXT, 52-week extension study of ENLIGHTEN-1; ENLIGHTEN-2-EXT, 52-week extension study of ENLIGHTEN-2; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; MMRM, mixed-model repeated measures; NA, not assessed; NNT, number needed to treat; OL, open-label; OLZ/SAM, a combination of olanzapine and samidorphan; PANSS, Positive and Negative Syndrome Scale; PK, pharmacokinetics; QT(c), (corrected) QT interval; R, DB, C, randomized, double-blind, controlled (placebo and/or active comparator) trial; SAE, serious adverse event; UGT, uridine 5'-diphospho-glucuronosyltransferase; WHO, World Health Organization.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

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antipsychotic-induced weight gain; the other patents are for the same indication and are a part of a subset/family), 16/899708 (pending), 17/071166, and 17/071236. The authors report no other conflicts of interest in this work.

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