**Supplemental Materials**

**Supplemental Table 1.** Descriptions of studies in the OLZ/SAMa clinical development program.

| **Study**  | **Design** **(duration)** | **Patient Population** | **No. of Patients** | **Interventions** **(mg/day)** | **Key Findings** |
| --- | --- | --- | --- | --- | --- |
| **Antipsychotic Efficacy Study** |  |  |  |  |
| ENLIGHTEN-1 (ALK3831-A305)61 | R,DB,C(4 weeksb)  | Adults with schizophrenia and a recent exacerbation of disease | 401 | * OLZ/SAM (10/10 or 10/20)
* Olanzapine (10 or 20)
* Placebo
 | * 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; *P*<0.001)
* 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, *P*=0.004)
* The LS mean change in PANSS total score from baseline to week 4 was −6.4 (*P*<0.001) with OLZ/SAM and −5.3 (*P*=0.004) with olanzapine
* LS Mean change in 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 provided significant improvements vs placebo (*P=*0.002 and *P*<0.001, respectively)
* Key safety findings are presented in Table 2
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| **Weight Efficacy Study** |  |  |  |  |
| ENLIGHTEN-2 (ALK3831-A303)62 | R,DB,C(24 weeksb) | Adults with schizophrenia | 561 | * OLZ/SAM (10/10 or 20/10)
* Olanzapine (10 or 20)
 | * Percent change in body weight from baseline to week 24 was 4.21% with OLZ/SAM and 6.59% with olanzapine, yielding a LS mean difference between OLZ/SAM and olanzapine of −2.38%; *P*=0.003 (co‑1° EP)
* Fewer patients gained ≥10% of their baseline body weight with OLZ/SAM vs olanzapine (17.8% vs 29.8%, respectively), such that patients had half the risk of clinically significant weight gain with OLZ/SAM vs olanzapine at week 24 (NNTc=8 ; odds ratio=0.50; *P*=0.003; co-1° EP)
* 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
* Proportion of patients who gained ≥7% of their baseline weight was significantly lower for OLZ/SAM at week 24 than for olanzapine (27.5% vs 42.7%; NNTc=7; odds ratio=0.50; *P*=0.001; 2° EP)
* 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])
* Proportion of patients with a waist circumference increase of ≥5 cm from baseline was 26.8% and 43.2% in the OLZ/SAM and olanzapine groups, respectively (NNTc=6 [95% CI: 4,13])
* The LS mean change from baseline to week 24 in PANSS total score was −8.2 with OLZ/SAM and −9.4 with olanzapine
* 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
* Key safety findings are presented in Table 2
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| **Phase 2 Supportive Efficacy and Safety Study** |  |  |  |
| Dose-finding study (ALK3831-302)60 | R,DB,Cd(12 weeksb) | Adults with schizophrenia | 309 | * Olanzapinee + placebo
* Olanzapinee + samidorphan (5)
* Olanzapinee + samidorphan (10)
* Olanzapinee + samidorphan (20)
 | * PANSS score changes were similar between groups: the 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)
* 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)
* Key safety findings are presented in Table 2
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| **Long-Term Safety and Durability of Treatment Effect Studies** |  |  |
| ENLIGHTEN-1-EXT (ALK3831-A306)74 | OL(52 weeksb) | Adults with schizophrenia | 277 | * OLZ/SAM (10/10, 15/10, or 20/10)
 | * Assessment of safety and tolerability were primary study objectives
* AEs occurred in 136 (49.1%) patients; most were mild or moderate in severity
* The most common AEs were weight increased (13.4%), somnolence (8.3%), nasopharyngitis (4.0%), and headache (4.0%)
* Mean change from baseline to week 52 in body weight was 1.86 kg
* Parkinsonism, akathisia, and dyskinesia occurred in 7%, 5%, and 3% of patients, respectively
* During the treatment and follow-up periods, 5 (1.8%) patients had suicidal ideation, suicidal behavior, or intentional overdose
* Mean PANSS total score was 78.9 (n=248) at study start
* Schizophrenia symptoms improved over 52 weeks of treatment, with PANSS total scores decreasing by 16.2 points at week 52
* 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)
 |
| ENLIGHTEN-2-EXT (ALK3831-A304)75  | OL(52 weeksb) | Adults with schizophrenia | 265 | * OLZ/SAM (10/10, 15/10, or 20/10)
 | * Assessment of safety and tolerability were primary study objectives
* Overall changes in weight, waist circumference, and metabolic laboratory parameters were small and remained stable during the extension
* In total, 60.8% of patients experienced any AE; the majority were mild or moderate in severity
* AEs occurring in ≥5% patients: weight decreased (8.7%), extra dose administered (7.9%), headache (6.8%), and weight increased (6.0%)
* Mean change from baseline to week 52 in body weight was −0.03 kg
* Rates of parkinsonism, akathisia, and dyskinesia were 4%, 2%, and 2%, respectively
* 6.8% of patients experienced suicidal ideation and 0.4% experienced the suicidal behavior
* These outpatients had a mean baseline PANSS total score of 59.0 (n=265)
* Mean PANSS total score remained stable (58.3 at week 52 in 168 patients with available assessments
* 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)
 |
| **Additional Studies** |  |  |  |  |  |
| Long-term follow-up safety (ALK3831-A308); NCT03201757 | OL(208 weeksb) | Adults with schizophrenia | 253f | * OLZ/SAM (5/10, 10/10, 15/10, or 20/10)
 | * This study is ongoing
* For patients with 12 months of data in this study as of April 1, 2019, schizophrenia symptoms remained stable (mean change from A308 baseline in CGI-S score was -0.09) and weight gain was limited (mean change from A308 baseline was 0.09 kg) with long-term OLZ/SAM treatment
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| ENLIGHTEN-Early (ALK3831-307); NCT03187769  | R,DB,C(12 weeksb) | Young adults with schizophrenia, schizo-phreniform disorder, or BD‑I with little cumulative exposure to antipsychotics | 425g | * OLZ/SAM (5/10, 10/10, 15/10, or 20/10)
* Olanzapine (5, 10, 15, or 20)
 | * This study is currently recruiting patients
* The main objectives are to assess the effects of OLZ/SAM and olanzapine on body weight as well as provide information on the safety/tolerability profiles of OLZ/SAM and olanzapine in individuals early in their illness
 |
| **Other Populations** |  |  |  |  |  |
| Treatment effects in schizophrenia and comorbid alcohol use disorder (ALK3831-401)73 | R,DB,C(42–66 weeksb) | Adults with schizophrenia and alcohol use disorder with a recent exacerbation of disease | 234 | * OLZ/SAMh
* Olanzapineh + placebo
 | * 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)
* There were no between-group differences in alcohol use behaviors, as measured by changes in WHO drinking risk level, number of heavy drinking days, or desire for alcohol
* 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)
* Key safety findings are presented in Table 2
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| **Clinical Pharmacology Studies** |  |  |  |
| *Bioequivalence* |  |  |  |  |  |
| Bioequivalence study (ALK3831-A101)64 | 3-period crossover, separated by 14-day washouts (≈8 weeks) | Healthy adults | 48 | * Single dose of OLZ/SAM (10/10), Alkermes olanzapine (10), or Zyprexa (10) on day 1 of each treatment period
 | * Olanzapine component of OLZ/SAM was bioequivalent to olanzapine and Zyprexa
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| *Pharmacokinetics With Potential Interaction* |  |  |
| Food effect (ALK3831-A107)67 | 2-period crossover separated by 14-day washout(≈4 weeks) | Healthy adults | 36 | * Single dose of OLZ/SAM (10/10) in fed and fasted conditions
 | * Food did not have a clinically relevant impact on the PK of olanzapine or samidorphan when given as OLZ/SAM
 |
| Effect of rifampin on PK of olanzapine and samidorphan (ALK3831-A103)65 | OL (≈5 weeks) | Healthy adults | 24 | * OLZ/SAM (10/10) on day 1 → rifampin (600) on days 15–21 → OLZ/SAM (10/10) with rifampin (600) on day 22 → rifampin (600) on days 23–28
 | * Coadministration of OLZ/SAM with rifampin decreased the total systemic exposure (AUC∞) of olanzapine and samidorphan by 48% and 73%, respectively
 |
| Effect of OLZ/SAM on PK of lithium or valproate (ALK3831-B101)68 | OL(≈4 weeks) | Healthy adults | 34 | * Lithium alone and coadministered with OLZ/SAMi
* Valproate alone and coadministered with OLZ/SAMj
 | * Coadministration of OLZ/SAM with lithium or valproate did not have a clinically significant effect on the PK of lithium or valproate
 |
| *Pharmacokinetics in Special Populations* |  |  |
| Hepatic impairment (ALK3831-A105)69 | OL(≈6 weeks) | Healthy and hepatically impaired adults (without psychiatric illness) | 20 | * Single dose of OLZ/SAM (5/10)
 | * In individuals with moderate hepatic impairment, there was an approximately 1.5-fold and 2.2-fold increase in AUC∞ and Cmax of olanzapine, respectively, and an approximately 1.5-fold increase in AUC∞ and Cmax of samidorphan compared with healthy controls
 |
| Renal impairment (ALK3831-A106)69 | OL(≈6 weeks) | Healthy and renally impaired adults (without psychiatric illness) | 20 | * Single dose of OLZ/SAM (5/10)
 | * In individuals with severe renal impairment, there was an approximately 1.5-fold and 2.3-fold increase in AUC∞ of olanzapine and samidorphan, respectively, and a <1.5-fold increase in Cmax for both olanzapine and samidorphan, compared with healthy controls
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| *Other Clinical Pharmacology Studies* |  |  |
| Cardiac safety (ALK3831-A109)70 | R,DB,C(≈4 weeks) | Adults with schizophrenia | 100 | * Moxifloxacin-matched placebo on days 1 and 14; OLZ/SAM on days 2–13 (10 /10 for 3 days, then 20/10 for 4 days, and then 30/30 for 5 days)
* Single dose of moxifloxacin (400) and moxifloxacin-matched placebo on days 1 and 14 (nested crossover fashion); OLZ/SAM-matched placebo on days 2–13
 | * OLZ/SAM, at doses up to supratherapeutic level (30/30 mg), did not have a clinically relevant effect on electrocardiogram parameters, including the QTc interval
 |
| Proof-of-concept study (ALK33-301)71 | R,DB,C (3 weeksb) | Healthy adults | 106 | * OLZ/SAM (10/5)
* Olanzapine (10)
* Samidorphan (5)
* Placebo
 | * Mean body weight change from baseline to last assessment (1° EP) was signiﬁcantly less for OLZ/SAM vs olanzapine (2.2 kg vs 3.1 kg, respectively; *P*=0.02)
* When administered in combination, samidorphan did not affect the PK of olanzapine and vice versa
 |
| PK study (ALK3831-A104)66 | OL (≈3 weeks) | Adults with schizophrenia | 42 | * Olanzapine (≤15) for 7 days → OLZ/SAM (10/10 or 20/10) thereafter
 | * Steady-state exposure to olanzapine increased dose proportionally over the clinical dose range of 10/10 mg to 20/10 mg of OLZ/SAM
* Different dose levels of olanzapine in OLZ/SAM had no effect on samidorphan exposure
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| Metabolic effects of OLZ/SAM (ALK3831-A108)72 | R,DB,C, exploratory (3 weeksb) | Healthy adults | 60 | * OLZ/SAM (10/10)
* Olanzapine (10)
* Placebo
 | * Olanzapine resulted in relative hyperinsulinemia and reduced insulin sensitivity during an OGTT at day 19, changes not observed with OLZ/SAM or placebo
* Insulin sensitivity, measured by hyperinsulinemic-euglycemic clamp, was decreased in all treatment groups relative to baseline; this effect was greatest with olanzapine and OLZ/SAM
* Postprandial (OGTT) glucose and fasting cholesterol concentrations were similarly increased with olanzapine or OLZ/SAM, but on other metabolic parameters, distinct effects were observed (eg, post-OGTT C-peptide concentrations; aspects of energy metabolism)
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aOLZ/SAM doses are given in the form X/Y, where X is the dose of olanzapine and Y is the dose of samidorphan.

bTreatment period.

cNNT values were calculated from the proportion of patients using a logistic regression model based on the multiple imputation for missing postbaseline assessments. Thus, the NNT and 95% CI values described here can differ from raw NNT estimates calculated from the actual rates provided.

dOlanzapine dosing was open label; the dose of coadministered samidorphan was blinded.

eOlanzapine was dosed per clinical judgement; the mean olanzapine dose/day across all treatment groups was 11–13 mg.

fEnrolled as of the April 1, 2019 data cutoff date.

gEstimated enrollment.

hDoses of study drug were selected by investigators; the mean prescribed olanzapine dose/day was 14–15 mg; the samidorphan dose was 10 mg.

iLithium (600 mg/day; 300 mg twice daily separated by 12 hours) on days 1–6 → lithium (300 mg) on day 7 → OLZ/SAM (10/10) on days 8–11 → OLZ/SAM (10/10) + lithium (600 mg/day; 300 mg twice daily separated by 12 hours) on days 12–17 → OLZ/SAM (10/10) + lithium (300 mg) on day 18.

jValproate (1000 mg/day; 300 mg twice daily separated by 12 hours) on days 1–6 → valproate (500 mg) on day 7 → OLZ/SAM (10/10) on days 8–11 → OLZ/SAM (10/10) + valproate (1000 mg/day; 500 mg twice daily separated by 12 hours) on days 12–17 → OLZ/SAM (10/10) + valproate (500 mg) on day 18.

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.90

1° EP, prespecified primary endpoint; 2° EP, prespecified secondary endpoint; AE, adverse event; AUC∞, area under the plasma concentration-time curve from time 0 to infinity; BD-I, bipolar I disorder; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; Cmax, maximum plasma concentration; EXT, extension; LS, least squares; NNT, number needed to treat; OGTT, oral glucose tolerance test; OL, open label; OLZ/SAM, combination of olanzapine and samidorphan; PANSS, Positive and Negative Syndrome Scale; PK, pharmacokinetics; QTc, QT interval corrected for heart rate; R, DB, C, randomized, double-blind, controlled (placebo and/or active comparator) trial; WHO, World Health Organization.

**Supplemental Table 2.** Proportion of patients with potentially clinically significant value shifts in lipid and glycemic parameters from baseline to week 24 in ENLIGHTEN-2.

| Shift category | OlanzapineAnytime, % / Sustained,a % | OLZ/SAMAnytime, % / Sustained,a % |
| --- | --- | --- |
| Fastingb Total cholesterol |  |  |
| ≥240 mg/dL | 14.9 / 2.5 | 17.5 / 0.9 |
| Increase ≥40 mg/dL | 27.4 / 5.3 | 26.4 / 4.0 |
| Fastingb HDL cholesterol |  |  |
| <40 mg/dL | 17.0 / 4.1 | 13.3 / 4.0 |
| Decrease ≥20 mg/dL | 15.6 / 3.4 | 17.4 / 4.5 |
| Fastingb LDL cholesterol |  |  |
| ≥160 mg/dL | 17.2 / 1.7 | 16.3 / 3.5 |
| Increase ≥30 mg/dL | 34.8 / 8.0 | 35.1 / 4.5 |
| Fastingb Triglycerides |  |  |
| ≥200 mg/dL | 28.7 / 5.6 | 25.7 / 4.4 |
| Increase ≥50 mg/dL | 58.1 / 11.4 | 57.7 / 11.7 |
| Fastingb Glucose |  |  |
| ≥126 mg/dL | 8.6 / 0 | 13.4 / 0.8 |
| Increase ≥10 mg/dL | 57.0 / 11.4 | 65.7 / 17.5 |
| HbA1c |  |  |
| ≥5.7% | 36.0 / 10.8 | 42.6 / 10.5 |

aSustained potentially clinically significant values refers to patients in whom the last 2 assessments through the end of treatment met potentially clinically significant criteria.

bFasting status was based on patient self-report without independent confirmation.

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLZ/SAM, combination of olanzapine and samidorphan.

**Supplemental Table 3.** Mean Changes From Baseline to Week 52 in Metabolic Parameters With Long-term OLZ/SAM Treatment in ENLIGHTEN-1-EXT or ENLIGHTEN-2-EXT.

| **Parameter** | **ENLIGHTEN-1-EXT** | **ENLIGHTEN-2-EXT** |
| --- | --- | --- |
| Total cholesterol (fastinga), mg/dL |
| Baseline, n | 276 | 265 |
| Mean (SD) | 191.8 (36.1) | 186.9 (37.2) |
| Week 52, n | 180 | 155 |
| Change from baseline, mean (SD) | 3.4 (31.2) | −2.4 (26.5) |
| LDL cholesterol (fastinga), mg/dL |
| Baseline, n | 276 | 265 |
| Mean (SD) | 120.4 (32.2) | 113.9 (33.7) |
| Week 52, n | 180 | 155 |
| Change from baseline, mean (SD) | 5.7 (28.8) | −1.5 (25.5) |
| HDL cholesterol (fastinga), mg/dL |
| Baseline, n | 276 | 265 |
| Mean (SD) | 51.7 (14.6) | 57.0 (19.5) |
| Week 52, n | 180 | 155 |
| Change from baseline, mean (SD) | 1.7 (12.9) | −1.3 (11.5) |
| Triglycerides (fastinga), mg/dL |
| Baseline, n | 276 | 265 |
| Mean (SD) | 141.7 (93.1) | 130.8 (88.8) |
| Week 52, n | 180 | 155 |
| Change from baseline, mean (SD) | 14.6 (70.1) | −10.7 (65.6) |
| Glucose (fastinga), mg/dL |
| Baseline, n | 276 | 265 |
| Mean (SD) | 94.3 (12.7) | 94.2 (14.1) |
| Week 52, n | 180 | 154 |
| Change from baseline, mean (SD) | 6.0 (14.4) | 1.3 (16.0) |
| HbA1c (%) |
| Baseline, n | 276 | 265 |
| Mean (SD) | 5.5 (0.4) | 5.5 (0.4) |
| Week 52, n | 181 | 168 |
| Change from baseline, mean (SD) | −0.07 (0.3) | 0.03 (0.3) |
| Insulin (fastinga), μIU/mL |
| Baseline, n | 275 | 265 |
| Mean (SD) | 15.4 (18.0) | 15.6 (24.7) |
| Week 52, n | 181 | 153 |
| Change from baseline, mean (SD) | −1.7 (14.8) | 2.5 (29.0) |

aFasting status was based on patient self-report without independent confirmation.

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLZ/SAM, combination of olanzapine and samidorphan; SD, standard deviation.

**Supplemental Figure 1.** Key pharmacokinetic findings: plasma concentrations (mean + SD) of olanzapine after a single dose of OLZ/SAM or Zyprexa (A)64; plasma concentrations (mean + SD) of lithium 300 mg (B) or valproate 500 mg (C) after administration alone or concurrently with OLZ/SAM 10/10 mg.68 OLZ/SAM, combination of olanzapine and samidorphan; SD, standard deviation.

**A.**



**B.**



**C.**

