Title

ALKS 3831 for Schizophrenia: Clinical Overview of Efficacy and Safety

Slide 1

Hello, I'm Cathy Southammakosane a medical officer in the FDA's Division of Psychiatry. I will be providing a clinical review of the efficacy and safety of ALKS 3831, a combination product with the addition of samidorphan to olanzapine intended to mitigate associated weight gain. This review was conducted in collaboration with the Division of Diabetes, Lipid Disorders, and Obesity.

Slide 2

The presentation will begin with brief overviews of olanzapine weight effects and of ALKS 3831 development. I will then discuss efficacy findings from a supportive phase 2 study and the two pivotal studies along with safety findings. This presentation will conclude with a clinical segue to the Office of Surveillance and Epidemiology discussion of concurrent opioid use concerns and a clinical summary.

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Schizophrenia and bipolar I disorder are severe, chronic mental illnesses, and second-generation antipsychotics constitute primary treatment options. There are numerous class safety issues for these antipsychotics including weight gain and metabolic effects. The incidence of adverse events varies within the class, but olanzapine, in particular, has a greater association with weight gain and metabolic disturbance. This table from olanzapine prescribing information illustrates these effects as proportions of patients gaining 7 or 15% of body weight in short- and long-term studies. Olanzapine-related weight gain has been described as rapid in the initial weeks of treatment, gradually slowing, then potentially plateauing after several months. Early weight gain may be a risk factor for substantial longer-term weight gain; additional potential risk factors for weight gain include lower baseline BMI, less prior exposure to antipsychotic medication, and younger age. The pathophysiology of this weight gain is unclear but is likely secondary to increased caloric intake; the pathophysiology of metabolic changes is similarly uncertain.

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ALKS 3831 is fixed-dose oral combination of olanzapine, which is in the atypical antipsychotic class as aforementioned, and samidorphan, which is a new molecular entity that functions as a mu opioid receptor antagonist. The proposed indications of schizophrenia and manic and mixed episodes and maintenance of bipolar I disorder match the approved indications for olanzapine. The Applicant proposes that the addition of samidorphan to olanzapine will reduce the weight gain commonly associated with olanzapine alone while preserving antipsychotic efficacy. Planned dosages are

olanzapine component 5 mg to 20 mg, again, matching approved olanzapine doses, each combined with samidorphan 10 mg.

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ALKS 3831 has not been approved in any country. During development there were several notable regulatory events. At the End-of-Phase-2 meeting, there was a discussion detailing further development to support product approval. The Division advised that at least two adequate and well-controlled studies would be necessary: First, a trial evaluating acute treatment of schizophrenia must demonstrate that the addition of samidorphan does not impair the antipsychotic efficacy of olanzapine as compared to placebo. Second, a trial would be required evaluating weight mitigation as compared to olanzapine over at least 6 months with an open-label extension of another 6 months.

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In a protocol assessment for this second study, the weight mitigation trial, the Division delineated that product approval would be based upon antipsychotic efficacy and significant weight gain mitigation. Significant weight mitigation must be supported by all of the listed parameters: the coprimary endpoints of mean percent weight change from baseline and categorical differences in weight change (specifically, proportion of subjects with $\geq$7 or 10% weight gain) and effect on metabolic laboratory results. Regarding the latter point, the Division was clear that if metabolic parameters worsened or showed no improvement, then this may argue against approval.

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This table displays the clinical trials under discussion in this presentation: 302, a phase 2 supportive study primarily evaluating antipsychotic efficacy with exploratory analysis of weight gain; A303 the phase 3 weight mitigation study; A305 the phase 3 antipsychotic efficacy study; and A304 and A306, long-term safety extension studies.

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In Study 302, 309 adult subjects with schizophrenia were randomized. This was a phase 2, proof-of-concept, dose-finding study. In the first 12 weeks, subjects were randomized to olanzapine plus placebo or olanzapine plus one of three samidorphan doses. This was followed by a 12-week active-controlled period. The primary efficacy endpoint was PANSS total score change from baseline during the 12-week double-blind treatment period. Exploratory endpoints included weight-related parameters.

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This figure illustrates the study design which consisted of two parts: Part A involved a 1-week olanzapine-only lead-in period during which subjects were titrated-to-effect between 5 mg and 20 mg then a 12-week, double-blind add-on treatment period. During the double-blind treatment period, subjects were randomized to samidorphan 5 mg, 10 mg, or 20 mg or to placebo. Part B was an active-control 12-week treatment period during which all subjects continued their established olanzapine dose and samidorphan—Subjects who were initially randomized to placebo were started on samidorphan 20 mg. Part B concluded with a 4-week open-label, olanzapine-only safety period. The focus of our review for this trial is on Part A.

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Subjects were between ages 18 and 50 years and with stable weight and BMI between 17 to 30 kg/m^2. They could not be antipsychotic naive, schizophrenia symptoms duration had to be >2 years, and initiation of first antipsychotic treatment had to be >1 year prior. Subjects with diabetes were excluded. Randomization was stratified by weight change in the 1-week olanzapine lead-in period so that two analysis populations were delineated in assessing weight gain: full-analysis set 1 included all subjects who were randomized, received at least one dose of study drug, and had at least one post-baseline PANSS assessment. Full-analysis set 2 included all full-analysis set 1 subjects who had also gained weight in the initial week of olanzapine lead-in treatment and who had at least one post-baseline weight assessment.

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With regards to the primary endpoint, changes in PANSS total scores were similar across all of the treatment groups and were corroborated by stable CGI-S scores: per the applicant's analysis, Pooled subjects on olanzapine with samidorphan had a mean change in PANSS total scores of -2.2 compared to subjects on olanzapine with placebo who had a mean change of -2.9.

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This figure illustrates the exploratory analysis of mean percent weight change by treatment arm over the 12-week treatment period in full-analysis set 1 subjects (again, these were subjects who were randomized and had at least one post-baseline PANSS assessment). The treatment difference between the olanzapine plus samidorphan groups compared to the olanzapine plus placebo group ranged from -1.2 to -1.9%. It appears that a samidorphan dose response was not observed, although note that this study was not designed to formally assess dose response.

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In this figure, which illustrates the exploratory analysis of mean percent weight change by treatment arm in full-analysis set 2 subjects (again, these were full-analysis set 1 subjects who gained any weight during the 1-week olanzapine lead-in period), a dose-dependent samidorphan effect was suggested. The treatment differences between the olanzapine plus samidorphan 10 mg and 20 mg groups compared to the olanzapine plus placebo group were -3.0% and -3.7%, respectively. The olanzapine plus samidorphan groups appear to separate from the olanzapine plus placebo group around Day 36.

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Study A303 was a phase 3 multicenter, randomized, double-blind, olanzapine-controlled study evaluating weight change; 561 adult subjects with schizophrenia were randomized. Notable enrollment criteria included: age 18 to 55 years, stable weight, BMI 18 to 30 kg/m^2; subjects could not be antipsychotic naive, were not permitted olanzapine use in the past 6 months, and could not have comorbid diabetes. Subjects were randomized to ALKS 3831, with fixed dose samidorphan 10 mg, or olanzapine only; all olanzapine doses were titrated from olanzapine 10 mg to 20 mg as tolerated. This was a 24-week outpatient trial. The coprimary endpoints were percent change in body weight and proportion of subjects with $\geq$10% weight gain.

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This figure illustrates the study design. The study schedule of assessments included: body weight and waist circumference at Screening, Baseline, Weeks 1 and 2, then every 2 to 4 weeks thereafter; metabolic labs at Baseline, Weeks 1, 2, and 4, then every 4 weeks thereafter; and quality of life questionnaires at Baseline and Weeks 4, 12, and 24. At the end of study, subjects were eligible to enroll in long-term open label Study A304 or entered a 4-week safety follow-up period. Subjects who prematurely discontinued study drug could attend monthly visits where weight, adverse events, and new antipsychotic use were elicited.

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Subject demographics and baseline characteristics revealed a preponderance of black males; mean age was 40 years; mean weight was 77 kg; and mean BMI was 25 kg/m^2. Demographic characteristics were reasonably balanced across treatment groups as were baseline weight parameters.

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The Applicant prespecified an unblinded interim analysis plan conducted by an independent statistician allowing for an increased sample size. During the analysis, conditional power for detecting a difference in the co-primary endpoints was assigned to one of three zones: favorable, with a conditional power of at least 90%, “promising,” with a conditional power between 30 and 90%, and unfavorable, with a

conditional power less than 30%. At the interim analysis, the conditional power for detecting a difference in the co-primary endpoints was 33% for percent change in body weight and 43% for the proportion of subjects with a ≥10% weight gain. Therefore, the Applicant increased their sample size by 140 subjects (70 per arm). The safety population consisted of 550 subjects who received at least one dose of study drug; the efficacy population consisted of 538 subjects who had at least one postbaseline weight assessment. There was a notable dropout rate of 36%, equal between the two treatment groups. Discontinuation due to adverse events was 12% in the ALKS 3831 group and 10% in the olanzapine group. 26% of subjects who had prematurely discontinued ALKS 3831 entered monthly visits compared to 20% of subjects who had prematurely discontinued olanzapine. Approximately half of these premature discontinuation subjects completed the monthly follow-up visits.

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Division of Diabetes, Lipid Disorders, and Obesity reviewers had recommended the coprimary endpoints of weight change from baseline and categorical analysis of proportion of subjects with a clinically relevant change in weight from baseline. In FDA draft guidance for industry, drug approval for weight loss in the treatment of obesity is based upon efficacy demonstrated by mean weight loss at least 5% greater than placebo or, on categorical analysis, at least double the number of subjects losing at least 5% body weight compared to placebo. Although a specific percent body weight gain has not been established to confer risk, weight loss of 5 to 10% has been demonstrated to improve metabolic parameters in obesity treatment. ALKS 3831 is not intended as a weight loss product, but we can use the approval standard for weight loss drugs as a reference.

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The first coprimary endpoint, percent weight change from baseline, was obtained by analysis of covariance; post-baseline missing values were handled by the multiple imputation method. There was a statistically significant weight gain mitigation effect when comparing ALKS 3831 to olanzapine. The difference in mean percent weight change from baseline between the two groups (or otherwise stated the treatment effect estimate) was -2.38% favoring ALKS 3831. Several sensitivity analyses also yielded similar estimates, which are not presented here. This accompanying figure suggests that ALKS 3831 weight mitigation effect is first observed at approximately 6 weeks of treatment.

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The second coprimary endpoint, the proportion of subjects who had $\geq$10% weight gain from baseline, was obtained by logistic regression model; post-baseline missing values were handled by the multiple imputation method. There was a statistically significant weight gain mitigation effect when comparing ALKS 3831 to olanzapine: 17.8% of subjects on ALKS 3831 versus 29.8% of subjects on olanzapine. This results in an estimated difference of 13.7% and an odds ratio of 0.50 favoring ALKS 3831. A key secondary endpoint was proportion of subjects who had $\geq$7% weight gain from baseline, which is a frequently cited antipsychotic-related weight gain cutoff in psychiatric literature. For this endpoint,

there was similar statistically significant weight mitigation effect in favor of ALKS 3831 with an estimated difference in proportions of -15.9% and an odds ratio of 0.50 favoring ALKS 3831.

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This accompanying figure shows a cumulative frequency distribution for percent change in weight amongst completers (64% of subjects completed the study). There is a favorable left shift for the ALKS 3831 group indicating lower probability of a specific weight gain percent for ALKS 3831 compared to olanzapine.

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Other weight-related endpoints were not controlled for type I error and so were presented descriptively. Mean changes in waist circumference were consistent with mean changes in weight. We will review glycemic changes in subsequent slides. Lipid changes were individually mixed but generally similar between the ALKS 3831 and olanzapine treatment groups. Blood pressure changes favored ALKS 3831 with a mean difference compared to olanzapine of -2.60 mmHg in systolic blood pressure and -0.70 mmHg in diastolic blood pressure at Week 24. Systolic blood pressure separation between groups appeared at Week 4 and persisted throughout treatment. While this blood pressure difference was small and may be spurious, prevention of even small increases over time is likely favorable for cardiovascular health

Slide 23

In some analyses, a glucose trend favoring olanzapine was suggested. This figure displays changes in mean fasting glucose across all timepoints in ALKS 3831 in green compared to olanzapine in blue. However, trends in mean hemoglobin A1c and insulin levels were similar between the two treatment groups.

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This first figure displays the higher proportions of subjects on ALKS 3831 shifting to high glucose levels at any time: 12% in ALKS 3831 subjects versus 9% in olanzapine subjects. Importantly, less than 1% of subjects on ALKS 3831 and none on olanzapine had sustained elevated glucose levels—This is defined as elevated levels at the last two study visits. The second figure displays the higher proportions of subjects on ALKS 3831 shifting to abnormal hemoglobin A1c at any time: 36% in ALKS 3831 subjects versus 31% in olanzapine subjects. The treatment difference was attributed to prediabetic range hemoglobin A1c abnormalities. These data are notable because of the more longitudinal nature of hemoglobin A1c percentages representing average glucose levels over 3 months. Nevertheless, 12% of ALKS 3831 subjects and 11% of olanzapine subjects had sustained hemoglobin A1c levels. Conversely, adverse events related to dysregulated glucose metabolism were greater with olanzapine at 8% compared to

ALKS 3831 at 4%. And more generally, these glycemic changes are of unclear clinical significance in the context of weight mitigation and metabolic disturbance in a population without diabetes mellitus.

Slide 25

With regard to quality of life measures, there were no differences between treatment groups in change from baseline in the Impact of Weight on Quality of Life total score and all five subscales and in EQ-5D, another quality of life measure, index score or visual analog scale. Of note, the Impact of Weight on Quality of Life measure is intended for use in patients with obesity. According to the Applicant, high baseline scores indicate that weight had a low impact on the subjects' quality of life at the start of the study.

Slide 26

In Study A305, 403 adult subjects experiencing acute schizophrenia exacerbations were randomized. Notable enrollment criteria included: age 18 to 70 years, PANSS score >80, and CGI >4; subjects were not antipsychotic naive and could not have olanzapine use in the past 6 months. This was a phase 3 international, randomized, double-blind, active- and placebo-controlled study evaluating antipsychotic efficacy. Subjects were randomized to ALKS 3831, olanzapine, or placebo; all olanzapine doses were titrated from olanzapine 10 mg to 20 mg as tolerated. This was a 4-week trial including a 2- to 4-week inpatient period. The primary endpoint was change in PANSS total score.

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This figure illustrates the study design as described. The study schedule of assessments included PANSS scores at Screening, Baseline, and weekly intervals. At the end of study, subjects were eligible to enroll in long-term open label Study A306 or entered a 2-week safety follow-up period.

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Subject demographics and baseline characteristics revealed a preponderance of white males from Eastern Europe, and mean age was 41 years. Small demographic imbalances between treatment arms for sex, race, and region are unlikely clinically significant. Baseline PANSS scores were similar across all three treatment groups.

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The safety population consisted of 401 subjects, and the efficacy population consisted of 397 subjects. The overall dropout rate was 12.2%, equal between the two active treatment groups.

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The primary endpoint, PANSS total score change from baseline, was obtained by mixed model with repeated measurements; there was no imputation of missing data. There was a statistically significant antipsychotic effect when comparing ALKS 3831 to placebo; the treatment difference in PANSS score change from baseline was -6.4 favoring ALKS 3831. These results were corroborated by CGI-S changes from baseline. Improvement was similar for olanzapine treatment.

Slide 31

Studies A304 and A306 evaluated 265 and 277 subjects, respectively. These were open-label, long-term, extension studies of Studies A303 and A305, respectively. All subjects received ALKS 3831 10 to 20 mg dosed to effect and as tolerated; there was no comparator arm. These were 52-week outpatient trials. The primary endpoints were safety and tolerability.

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In this figure, switching effect on weight was assessed at the transition period from Studies A305 to A306 (denoted Group 1). The transition periods extended to 12 weeks after switch. In Group 1, subjects switching from olanzapine or placebo to ALKS 3831 demonstrated initial increase in weight trajectory with stabilization at approximately 4 to 6 weeks after medication switch.

Slide 33

In this figure, switching effect on weight was assessed at the transition period from Studies A303 to A304 (denoted Group 2). In Group 2, data from subjects switching from olanzapine to ALKS 3831 suggested initial increase in weight trajectory with stabilization at approximately 28 weeks after medication switch. Historical olanzapine data suggest that weight gain trajectory may continue to increase over time whereas long-term ALKS 3831 data potentially suggests less weight gain over time.

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In Studies A304 and A306, metabolic laboratory parameters were also monitored as part of the safety assessment. Lipid and glycemic changes were similar or favorable when comparing subjects on ALKS 3831 to subjects from historical olanzapine data.

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Interpretation of long-term ALKS 3831 data is limited by the following: the data was selective including only subjects who chose to enroll in the open-label studies, comparator arms were absent, there was a significant proportion of missing data, and one open-label study was ongoing at the time of data lock.

Additionally, comparison to historical data must be interpreted with similar caution because of the general limitations of cross-study comparisons. Subject characteristics or other factors to support interpretation were not described.

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ALKS 3831 shares a similar class safety profile to other atypical antipsychotics, and there were no new safety signals. Across the various ALKS 3831 development programs, there were three deaths that were unrelated to study treatment. In Studies A303 and A305, rates of serious adverse events were similar between the active treatment groups, ALKS 3831 and olanzapine, ranging from 1% to 4%. Adverse events leading to discontinuation of study drug occurred at similar rates between the two active treatment groups and at a lower rate than in the placebo group in Study A305. Adverse events leading to discontinuation occurring at a rate of >1% in the active treatment groups were somnolence in the ALKS 3831 group and glycosylated hemoglobin increased in the olanzapine group, each at 2%.

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Common adverse events occurring in $\geq$5% of subjects receiving ALKS 3831 are seen here; of these, somnolence, dry mouth, and fatigue occurred more frequently with ALKS 3831 treatment than with olanzapine treatment.

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Investigations revealed disturbances in laboratory results and vital signs—most are likely representative of class effects and most differences in occurrences with ALKS 3831 compared to olanzapine were small. Weight change and metabolic effect were discussed earlier in this presentation. Other observed class effects included: disruptions in liver enzyme levels, prolactin levels, and neutrophil and leukocyte values, orthostatic hypotension, QTc shifts, and extrapyramidal symptoms.

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An important safety consideration for ALKS 3831 is the potential for samidorphan's opioid antagonist mechanism of action lending to risks of precipitated opioid withdrawal in patients who are opioid dependent, ineffective analgesia when opioids are medically necessary, and opioid overdose if a patient were to attempt to overcome the samidorphan opioid antagonist effect. Opioid use was an exclusion criterion for ALKS 3831 clinical studies, so assessment for these risks was limited. Clinical data included precipitated opioid withdrawal and subsequent hospitalization in one subject taking samidorphan 10 mg who was enrolled in a phase 1 samidorphan-only trial. This trial enrolled subjects who were opioid-experienced but not -dependent, but this subject did not disclose his opioid-dependence history at Screening. Eighteen subjects on ALKS 3831 reported concomitant opioid exposure; of these subjects, two were exposed to opioids for more than short-term durations. There were no reports of inadequate analgesia. Limitations include non-rigorous means of obtaining and assessing this information. Three

subjects on ALKS 3831 were documented with opioid abuse adverse events. Two of the subjects had urine drug screens positive for opiates and other substances; a third subject reportedly misrepresented cannabis use as heroin abuse to gain hospital admission—There was no drug screen available for confirmation. Finally, there was one subject hospitalized for a reported accidental opioid overdose that was confirmed by drug testing. The Office of Surveillance and Epidemiology reviewer will follow this presentation with epidemiological data as further context for concerns with concurrent opioid use with ALKS 3831 treatment.

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In conclusion, ALKS 3831 has demonstrated evidence of antipsychotic efficacy for treatment of schizophrenia, and there are no new safety signals although potential concerns associated with samidorphan opioid antagonism in real-world settings does exist.

Slide 41

In Study A303, the 24-week randomized, active-controlled trial, the coprimary and key secondary endpoints were: a mean weight gain difference of -2.4% of baseline body weight, 18% of ALKS 3831 subjects compared to 30% of olanzapine subjects gaining $\geq$10% of baseline body weight, and 28% of ALKS 3831 subjects compared to 43% of olanzapine subjects gaining $\geq$7% of baseline body weight. Interpretation of these results is limited by missing data with a 36% dropout rate in both treatment groups and by absence of a long-term olanzapine-only control arm. Waist circumference differences were consistent with weight change. Systolic blood pressure changes favored ALKS 3831; the difference was small and may be spurious, but prevention of even small increases over time is likely favorable for cardiovascular health. There were no consistent trends of benefit in lipid and glycemic parameters rather some glycemic laboratory results trended adversely. In the supportive phase 2 proof-of-concept Study 302, the 12-week randomized, active-controlled trial, preceded by a 1-week olanzapine run-in period, weight was an exploratory endpoint. Overall, the difference in olanzapine-subtracted weight change was not clearly dose-related, ranging from -1.2 to -1.9%. No additional, meaningful information was provided regarding waist circumference measurement, metabolic laboratory trends, or blood pressure measurement data.

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This concludes the clinical review of ALKS 3831 efficacy and safety; thank you for your attention.

Title: Consideration of Potential Risks Associated with ALKS 3831 in Real World Settings of Opioid Use

Slide 1:

Good afternoon. My name is Celeste Mallama, I'm an epidemiologist at FDA, and I will be presenting on consideration of potential risks associated with ALKS 3831 in real world settings of opioid use.

Slide 2:

The objective of this presentation is to provide a brief overview of epidemiologic, surveillance, and drug utilization data to inform discussion of the potential risks associated with this product, which contains a new opioid antagonist, in the setting of acute or chronic opioid use, either medical or nonmedical, and discuss proposed mitigation of these risks.

Slide 3:

For general context, we analyzed recent antipsychotic use patterns from U.S. retail and long-term care pharmacies and observed that olanzapine accounted for approximately twelve percent, or 7 million, of the 64 million antipsychotic prescriptions dispensed in 2019.

Slide 4:

Potential risks associated with use of ALKS 3831 in real world settings of opioid use include: opioid withdrawal, inadequately controlled pain, and opioid overdose.

Slide 5:

The first risk scenario involves precipitated opioid withdrawal, which occurred in one subject during the clinical development program. If a prescriber is unaware that a patient initiating ALKS 3831 is opioid dependent, either through medical or nonmedical chronic opioid exposure, use of samidorphan could precipitate opioid withdrawal.

Slide 6:

To better understand the proportion of the indicated population who might be at risk for this adverse event, we examined data on chronic opioid use, non-medical use, and opioid use disorder in patients with bipolar disorder and schizophrenia.

In a 2015-2016 health system sample, chronic opioid use was three times more common in patients with bipolar disorder compared to patients with no mental health disorder.

Individuals with bipolar disorder also have a higher risk of opioid nonmedical use and opioid use disorder. Based on limited national survey data, potentially greater than 5% of patients with bipolar disorder use opioids nonmedically, and potentially 1-3% have an opioid use disorder.

Slide 7:

Evidence is mixed on whether chronic pain and opioid use are more common with schizophrenia, and data are sparse on nonmedical opioid use or opioid use disorder in U.S. patients with schizophrenia. Older survey data suggest that opioid nonmedical use is higher in patients with schizophrenia compared to those without a mental health disorder.

Slide 8:

Because samidorphan has never been marketed, we have no real world data on precipitated withdrawal or other adverse events associated with concomitant opioid use. To better characterize this potential risk, we reviewed cases reported to FDA adverse event reporting system related to bupropion/naltrexone, which is approved for chronic weight management, as this product also contains an orally bioavailable opioid antagonist and is contraindicated with opioid use**.** We recognize, however, that these are two different products used for different indications.

In 2019, approximately 341,000 prescriptions for bupropion/naltrexone were dispensed from U.S. outpatient retail pharmacies.

From December 2016 to August 2020, we identified 13 cases of suspected opioid withdrawal associated with concurrent use of at least one opioid product and bupropion/naltrexone.

The majority of these cases reported hospitalization.

The limitations of FAERS must be kept in mind. This is a case series of adverse events resulting from a potential drug-drug interaction between bupropion/naltrexone and an opioid. These cases are only those that were spontaneously reported to FAERS and particularly, as this is a labeled adverse event, these do not likely represent the totality of events occurring in the patient population.

Slide 9:

Another potential scenario is a patient taking ALKS 3831 who develops a severe pain condition requiring opioid analgesics. Because of samidorphan's opioid receptor antagonism, the analgesic effect of the opioid could be reduced. While there were no reports of inadequately controlled pain in clinical trial patients who received opioids, this represented a relatively small number of patients and data were not prospectively collected on pain control or how opioids were actually taken.

Slide 10:

To better understand what proportion of patients might require opioids while taking ALKS 3831, we examined overlapping prescriptions for olanzapine and opioid-containing products. In 2019, approximately 21% of patients on olanzapine received a concurrent prescription for an opioid from outpatient pharmacies.

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Again, because we have no postmarket data related to samidorphan, we looked at reports of inadequately controlled pain in patients taking bupropion/naltrexone which contains an orally bioavailable opioid antagonist.

Based on drug utilization data from September 2014 to August 2016, 11% of patients receiving bupropion/naltrexone had a concurrent claim for a select opioid despite their contraindication in product labeling. From December 2016 to August 2020, one case was reported to FAERS describing reduced analgesic effect in a patient taking concurrent bupropion/naltrexone and an opioid product.

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Last, we will discuss two scenarios that could potentially lead to an increased risk of opioid overdose.

The first scenario is a patient with acute pain who attempts to overcome samidorphan's antagonist blockade by increasing their opioid dose, potentially exposing them to a high dose of unopposed opioid agonist as the samidorphan effect wanes (for instance, if therapy is interrupted or discontinued).

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The second scenario that could potentially increase the risk of an opioid overdose is a patient who tapers off chronic opioids to initiate ALKS 3831, and later discontinues ALKS 3831, resuming opioid use at their previous dose, possibly increasing their risk of opioid overdose due to loss of opioid tolerance.

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Again, because samidorphan is not currently marketed, we looked at opioid overdose in individuals treated with oral naltrexone, an orally bioavailable opioid antagonist. In studies of patients with opioid use disorder treated with oral naltrexone, overdose risk was higher immediately following cessation of oral naltrexone, compared with during treatment or greater than 4 weeks after discontinuing treatment, indicating that there is a period of higher risk directly after discontinuation of oral naltrexone.

It's important to note however, that overdose risk is likely lower in the ALKS 3831 proposed patient population than in individuals with opioid use disorder.

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The Applicant has proposed to mitigate the risks of opioid withdrawal, inadequate pain control, and potential for opioid overdose through labeling.

Labeling will include a contraindication for patients who are dependent on opioids or patients with chronic opioid use. There will also be a Warning and Precaution to alert prescribers that patients receiving opioids should be opioid-free prior to treatment; if opioid therapy is needed, ALKS 3831 should be stopped and another antipsychotic should be considered; and patients with prior opioid use may be more sensitive to opioids after treatment discontinuation.

Lastly, the Medication Guide will include information for patients on these risks and safe use of ALKS 3831.

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In conclusion, potential safety concerns related to samidorphan's opioid antagonist effect in real-world settings of opioid use warrant consideration.

Epidemiologic data suggest that a non-trivial proportion of the indicated population may be exposed to opioids and be vulnerable to these potential risks.

If approved, it is possible that these risks could be mitigated through labeling alone, however we welcome the committee's input.

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Thank you.