FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting

October 9, 2020

Topic: New Drug Application 213378

ALKS 3831 (olanzapine/samidorphan) for the treatment of schizophrenia and bipolar I disorder
The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committees. The FDA background package contains assessments or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final positions of the individual reviewers, review Divisions, or Office. FDA has brought New Drug Application 213378, ALKS 3831 (olanzapine/samidorphan) for the treatment of schizophrenia and bipolar I disorder, to these Advisory Committees in order to gain the Committees’ insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and, instead, is intended to focus on issues identified by FDA for discussion by the Advisory Committees. FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.
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<td>AE</td>
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Alkermes (the Applicant) has developed ALKS 3831, a fixed-dose oral combination of olanzapine and samidorphan, taken daily for the treatment of schizophrenia and for bipolar I disorder (acute treatment of manic or mixed episodes/maintenance treatment/as an adjunct to valproate or lithium in the treatment of manic or mixed episodes). Olanzapine is an atypical antipsychotic initially approved in 1996 for the treatment of schizophrenia in adults. Samidorphan is a new molecular entity that functions as a mu opioid receptor antagonist with low agonist activity at kappa and delta opioid receptors. The Applicant hypothesizes that samidorphan can reduce the weight gain and metabolic adverse reactions commonly associated with olanzapine without compromising the therapeutic antipsychotic benefits of olanzapine or causing unacceptable risk.

In this document, when dosing of ALKS 3831 is discussed, the first milligram strength (before the slash) is the olanzapine strength; the second milligram strength (after the slash) is the samidorphan strength. For example, ALKS 3831 (20 mg/10 mg) indicates olanzapine 20 mg/samidorphan 10 mg.

The ALKS 3831 development program comprised a phase 2 dose-ranging study, two phase 3 efficacy and safety studies, and several open-label extension studies without a comparator. The phase 3 studies were:

- Study A303 was a 24-week randomized (1:1), double-blind comparison of ALKS 3831 (10 mg/10 mg) or (20 mg/10 mg) to olanzapine 10 mg or 20 mg in people with schizophrenia.
Coprimary\(^1\) endpoints were the percent change from baseline in body weight and the proportion of subjects with 10% or more weight gain from baseline, both at week 24. This study was intended to demonstrate that the addition of samidorphan to olanzapine could meaningfully prevent olanzapine-associated weight gain.

- Study A305 was a 4-week randomized (1:1:1), double-blind comparison of ALKS 3831 (10 mg/10 mg) or (20 mg/10 mg) to olanzapine 10 mg or 20 mg and placebo in people with schizophrenia. The primary endpoint was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) at week 4. This study was intended to demonstrate that the addition of samidorphan did not meaningfully impair the antipsychotic efficacy of olanzapine.

In Study A303, using the Applicant’s primary multiple imputation analysis, the mean change-from-baseline in weight between groups (ALKS 3831 – olanzapine) at week 24 was -2.38% (unadjusted 95% confidence interval (CI): -3.88%, -0.88%; \(p=0.002\)). The proportions of subjects with weight gain of 10% or more from baseline at week 24 was 17.8% in the ALKS 3831 group and 29.8% in the olanzapine group (\(p=0.003\)).

Drugs approved for weight loss in the treatment of obesity are found to be effective if mean weight loss is at least 5% greater than placebo or, on categorical analysis, at least two-times more subjects on drug lose at least 5% body weight as compared to those on placebo; see the 2007 FDA draft guidance for industry, *Developing Products for Weight Management*. ALKS 3831, however, is not intended as a weight loss product; instead, samidorphan is intended to mitigate the adverse reaction of weight gain commonly caused by olanzapine, and the contribution of samidorphan to the ALKS 3831 fixed-dose combination product must be examined in that context. In other words, the approval standard for weight loss drugs can be used as a reference but does not represent the standard for establishing the contribution of samidorphan. That standard is whether samidorphan meaningfully mitigates the weight gain caused by olanzapine. Although a specific percent of body weight gain has not been established to confer risk, because weight loss of 5 to 10% has been demonstrated to improve metabolic parameters in the treatment of obesity, an assumption that 5 to 10% weight gain has deleterious effects on health is reasonable.

A major reason for concern about weight gain with olanzapine and other second-generation antipsychotics is its relationship to metabolic syndrome. The weight-related metabolic parameter endpoints of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting blood sugar, HbA1c, and insulin were included in Study A303 and there was no appreciable difference between the ALKS 3831 group and the olanzapine-only group. Whether mitigation of weight gain, absent a coincident improvement in metabolic parameters, would be considered clinically meaningful is the main question for the committees.

Antipsychotic efficacy was not a primary endpoint in Study A303; however, efficacy was suggested by LS mean change from baseline PANSS total scores of -8.2 in the ALKS 3831 group and -9.4 in the olanzapine group and by CGI-S change from baseline in each group. In Study A305, mean change from baseline PANSS total score was -19.4 in the placebo group,

\(^1\) i.e., efficacy needed to be demonstrated on both primary endpoints
-23.7 in the ALKS 3831 group, and -22.4 in the olanzapine group; LS mean difference between ALKS 3831 and placebo treatment was -6.4. These primary findings were corroborated by CGI-S changes from baseline.

There are potential safety risks that need to be considered with the inclusion of samidorphan in the fixed-dose combination product: whether samidorphan’s opioid-antagonist action may precipitate withdrawal in patients who are physically dependent on opioids and whether samidorphan use could lead to ineffective analgesia when opioids are medically necessary or inadvertent blocking of a high in those with an opioid use disorder. These latter situations could result in overdose as a patient attempts to overcome samidorphan’s opioid antagonist effects.

This joint meeting of the PDAC and DSARM will focus on issues critical to the Center for Drug Evaluation and Research (CDER) assessment of whether ALKS 3831 (olanzapine/samidorphan) is safe and effective.

The following are points under consideration:

1. Has the Applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain?

2. Has the Applicant adequately characterized the safety profile of ALKS 3831?

3. Is labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan?

4. What, if any, additional data are needed to address outstanding issues?
2. OBJECTIVE OF MEETING AND OVERVIEW OF DEVELOPMENT PROGRAM

2.1. PURPOSE

The purpose of this Advisory Committee meeting is to obtain input from the committees on the efficacy, safety, and benefit:risk profile of ALKS 3831 (olanzapine and samidorphan) oral tablets as submitted by Alkermes under new drug application (NDA) 213378 for the following proposed indications in adult patients:

- Treatment of schizophrenia
- Treatment of bipolar I disorder
  - Acute treatment of manic and mixed episodes
  - Maintenance treatment
  - Adjunct to valproate or lithium in the treatment of manic or mixed episodes

For ease of reference, the specific bipolar disorder-related indications will be referred to as “treatment of bipolar I disorder.”

The committees will be asked whether data provided by the Applicant suggest a favorable benefit:risk profile for ALKS 3831 that would support approval with information on weight mitigation in labeling.

2.2. PRODUCT UNDER REVIEW

ALKS 3831 is a fixed-dose oral combination of olanzapine and samidorphan developed for the treatment of schizophrenia and bipolar I disorder.

Olanzapine is an atypical antipsychotic that was initially approved in 1996 (as Zyprexa, NDA 020592) for the treatment of schizophrenia in adults; it is available in the United States in multiple oral and injectable formulations with indications for schizophrenia and bipolar I disorder, and, in combination with fluoxetine, for acute depressive episodes associated with bipolar I disorder and treatment-resistant depression. Samidorphan is a new molecular entity that functions as a mu opioid receptor antagonist with low agonist activity at kappa and delta opioid receptors.

The Applicant hypothesizes that combining samidorphan with olanzapine will reduce the weight gain and metabolic adverse reactions commonly associated with olanzapine use while continuing to deliver the therapeutic antipsychotic benefits of olanzapine. The proposed fixed-dosage strengths formulated in bilayer tablets are 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg.

2.3. ANTIPSYCHOTIC METABOLIC CONSIDERATIONS

Schizophrenia and bipolar I disorder are severe and chronic mental illnesses each affecting approximately 1% of the population (American Psychiatric Association 2013). The most recent
APA practice guideline for the treatment of schizophrenia recommends that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued through the stable maintenance phase of the illness to reduce the risk of relapse (Lehman et al. 2004). In terms of pharmacological treatment for bipolar I disorder, the mood stabilizer mainstays of lithium and the antiepileptic valproate have been joined by multiple “atypical” or second-generation antipsychotics and the mood stabilizer antiepileptics lamotrigine and carbamazepine extended-release capsules (American Psychiatric Association 2002). Despite these numerous approved treatments, an individual patient may require several trials with different drugs before a tolerable effective treatment is identified.

Relevant class safety issues for antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, seizures, blood dyscrasias, and increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis. The second-generation antipsychotics have been associated with more weight gain, hyperglycemia/diabetes mellitus, and dyslipidemia compared to the “typical” or first-generation antipsychotics and may contribute to cardiometabolic disease burden in this vulnerable patient population (Olsson et al. 2015). Within each class of typical or atypical antipsychotic (and across individual antipsychotics), the incidence of these adverse effects varies.

Olanzapine, in particular, has been associated with weight gain, hyperglycemia/diabetes mellitus, and dyslipidemia. In a landmark study of almost 1,500 patients with schizophrenia randomized to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months, patients treated with olanzapine were generally less likely to discontinue treatment for any cause (indicating, to some degree, antipsychotic efficacy); however, significantly more patients on olanzapine discontinued drug due to adverse events—primarily due to weight gain and metabolic effects (9% versus 1% to 4% for the other drugs) (Lieberman et al. 2005).

Weight gain and metabolic effects are listed in the Warnings and Precautions section of the olanzapine prescribing information. Weight gain from clinical trials in adults is described as follows:

<table>
<thead>
<tr>
<th>Weight Gain from Clinical Trials</th>
<th>OLZ</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>13 placebo-controlled olanzapine monotherapy studies</td>
<td>+2.6 kg</td>
<td>-0.3 kg</td>
</tr>
<tr>
<td>Mean weight change, median 6 weeks</td>
<td></td>
<td></td>
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<tr>
<td>Proportion 7% weight gain, median 8 weeks</td>
<td>22.2%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Proportion 15% weight gain, median 12 weeks</td>
<td>4.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Weight gain discontinuation</td>
<td>0.2%</td>
<td>0%</td>
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Long-term studies, at least 48 weeks, median 573 days, N=2021

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<th>Weight Gain from Clinical Trials</th>
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<tbody>
<tr>
<td>Mean weight change</td>
<td>+5.6 kg</td>
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</tr>
<tr>
<td>Proportion 7% weight gain</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Proportion 15% weight gain</td>
<td>32%</td>
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<td>Proportion 25% weight gain</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Weight gain discontinuation</td>
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Source: Zyproxa prescribing information
Abbreviations: N = number of subjects, OLZ = olanzapine
The Applicant reports that certain patients appear to be at greater risk from olanzapine-induced weight gain, such as those with a lower body mass index (BMI), those with less prior exposure to antipsychotics, and younger patients.²

Weight gain with olanzapine has been described as rapid during the first few weeks, slowing gradually, and plateaing after several months (Hasnain et al. 2012). Weight gain in the first few weeks of olanzapine treatment is associated with longer-term weight gain (Lipkovich et al. 2006). As described in one paper, patients who experienced early weight gain were more than three times as likely to experience meaningful long-term weight gain as those who did not experience early weight gain (Lipkovich et al. 2008).

The 3-year prospective, nonrandomized observational European Schizophrenia Outpatient Health Outcomes (SOHO) study (Novick et al. 2009) illustrates the trajectory of weight gain over time with olanzapine versus other antipsychotic drugs. The study evaluated adverse effects, including weight gain, over time in adult patients who started an antipsychotic (olanzapine, risperidone, quetiapine, amisulpride, clozapine, oral/depot typical antipsychotics) for the outpatient treatment of schizophrenia. This particular posthoc analysis was limited to 4,939 patients who started monotherapy. The majority of patients in the study (55%) took olanzapine, and 65% of olanzapine patients completed the study. Weight gain was reported to occur in all groups but was greatest with olanzapine (Figure 1).

Figure 1. Mean Weight Change at Each Visit by Treatment Cohort, European SOHO Observational Study

![Figure 1](image)

Source: (Novick et al. 2009), Figure 1; quetiapine-treated patients had a higher BMI at baseline.

Abbreviations: SOHO = Schizophrenia Outpatient Health Outcomes

² NDA 213378, Integrated Summary of Efficacy (ISE)
2.4. REGULATORY BACKGROUND

ALKS 3831 has not been approved or marketed in any country. In 2012, the Applicant opened Investigational New Drug (IND) application 114375 for the prevention of olanzapine-induced weight gain in the Division of Diabetes, Lipids, and Obesity (DDLO). DDLO and the primary review division (DP) agreed that the IND should reside in DP, and it was transferred in 2013.

In 2015, FDA met with the Applicant for an end-of-phase 2 meeting to discuss the nonclinical and clinical development plans to support product approval of ALKS 3831 as a treatment for schizophrenia. The Division advised the Applicant that a minimum of two studies of different types would be necessary for approval. First, a three-arm, 4-week to 8-week study of the effectiveness of ALKS 3831 in the acute treatment of schizophrenia was necessary to demonstrate the addition of samidorphan did not impair the antipsychotic efficacy of olanzapine. The three treatment arms would include ALKS 3831, placebo, and olanzapine. The primary outcome variable needed to measure schizophrenia symptoms (e.g., PANSS), and ALKS 3831 would need to demonstrate its superiority over placebo. The second study would be a randomized, olanzapine-controlled study monitoring weight change for at least 6 months, with an open-label extension of 6 months.

On September 25, 2015, the Applicant submitted a special protocol assessment for Study A303, an assessment of weight gain on ALKS 3831 compared to olanzapine in adults with schizophrenia. The primary endpoint was the percent change in weight at Week 24; the proportion of subjects with ≥10% weight gain at Week 24 was a secondary endpoint. The Division sent a Special Protocol Assessment No Agreement letter to the Applicant requiring that the percent change in weight and the proportion of subjects meeting a certain threshold of weight gain be coprimary endpoints (i.e., superiority on both endpoints required for the study to be deemed positive), which the Applicant incorporated in their subsequent study design.

The Division also stated in this letter that “if metabolic parameters worsen or show no improvement, then this may argue against approval in the review of the combination drug product” and “the final approval decision may also depend on other [sic] important aspects of drug effect, i.e., the effects on laboratory based metabolic parameters and possibly schizophrenia symptoms.”

The Applicant submitted the NDA on November 15, 2019, it was filed on January 14, 2020, with a standard review priority.
## 3. SUMMARY OF CLINICAL DATA

### 3.1. EFFECTIVENESS OF ALKS 3831

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| ALK3831-302 | Phase 2:  
Randomized, double-blind, placebo-controlled  
Part A:  
1-week open-label olanzapine lead-in  
12-week double-blind samidorphan addition  
Part B:  
12-week open-label olanzapine and samidorphan  
4-week open-label olanzapine follow-up | Olanzapine 5 mg, 10 mg, 15 mg, or 20 mg based on individual titration | Primary: Change in PANSS from randomization to end of Part A (12 weeks) | 309 |
| ALK3831-A303 | Phase 3:  
24 weeks  
Randomized, double-blind, olanzapine-controlled  
Weight mitigation study | Randomized 1:1 to ALKS 3831 (10 mg/10 mg), (20 mg/10 mg) or Olanzapine 10 mg, 20 mg | Coprimary: Percent change in body weight from baseline to week 24 | 561 |
| ALK3831-A305 | Phase 3:  
4 weeks  
Randomized, double-blind, olanzapine- and placebo-controlled  
Antipsychotic efficacy study | Randomized 1:1:1 to ALKS 3831 (10 mg/10 mg), (20 mg/10 mg) or Olanzapine 10 mg, 20 mg or Placebo | Primary: PANSS change from baseline to week 4 | 403 |
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<th>Daily Dosage</th>
<th>Study Endpoints</th>
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<td>ALKS 3831</td>
<td>Safety</td>
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<td></td>
<td>Open-label (ALKS 3831) extension of A303</td>
<td>10mg/10mg</td>
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<td>15mg/10mg</td>
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<td>20mg/10mg</td>
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<tr>
<td>ALK3831-A306</td>
<td>Phase 3</td>
<td>ALKS 3831</td>
<td>Safety</td>
<td>281</td>
</tr>
<tr>
<td></td>
<td>Open-label (ALKS 3831) extension of A305</td>
<td>10mg/10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15mg/10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20mg/10mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: FDA clinical reviewer
Abbreviations: PANSS = Positive and Negative Syndrome Scale
3.1.1. Study ALK3831-302

This was a phase 2, proof-of-concept, safety, tolerability, dose-finding, randomized, placebo-controlled, multicenter study of samidorphan in people with schizophrenia on olanzapine. The primary objective was to evaluate whether three potential doses of samidorphan, in combination with olanzapine, produced similar antipsychotic efficacy as olanzapine alone as measured by the PANSS after 12 weeks of treatment. Exploratory objectives included the assessment of weight and metabolic parameters.

3.1.1.1. Trial Design

Study 302 was conducted in two parts:

- Part A included a screening period; a 1-week olanzapine-only lead-in period; and a 12-week, double-blind, samidorphan versus placebo add-on treatment period. Subjects who completed the lead-in period continued their established dose of olanzapine (5 mg, 10 mg, 15 mg, or 20 mg) and were randomized in a 1:1:1:1 ratio to one of the three strengths of samidorphan (5 mg, 10 mg, or 20 mg) or placebo. Randomization was stratified by the amount of weight change during the olanzapine-only lead-in period: ≤0 kg, >0 kg to <1 kg, or ≥1 kg. Subjects who were taking antipsychotic medication during screening were tapered off of their prior antipsychotic treatment within 2 weeks after initiation of the olanzapine open-label period (i.e., by day 15).

- Part B included a 12-week treatment period during which all subjects received their established dose of olanzapine and samidorphan. Subjects who had received samidorphan during part A continued their previous dose; subjects who had received placebo were started on samidorphan 20 mg. After 12 weeks, all samidorphan was discontinued and open-label olanzapine was continued for a 4-week safety period.

The primary efficacy endpoint was change from randomization (Day 8) to Day 92 in PANSS total score, that is, change from baseline over the 12 weeks double-blind period. The primary analysis was to explore whether the effect of olanzapine plus samidorphan (when all three doses were pooled) was equivalent to that of olanzapine plus placebo based on a pre-specified equivalence margin of 10 points. Of note, although a non-inferiority (NI) design would not be acceptable in a study intended to support a marketing application given that the secular trend for increasing placebo response over time makes it impossible to determine an appropriate NI margin for schizophrenia,³ the Division felt that this 10-point margin was reasonable in the context of a proof-of-concept study.

Two analysis populations were used for describing effects on weight:

- The full-analysis set (FAS) 1 population included all subjects who were randomized, received at least one dose of study drug, and had at least one post-baseline PANSS assessment.

• The FAS 2 population was an outcome-driven subgroup, defined as all FAS 1 subjects who gained weight during the initial week of olanzapine treatment prior to randomization and who had at least one post-baseline weight assessment.

**Figure 2. Schematic of Study 302**

```
Screening/baseline (Day 30 to 1) →
1-week olanzapine lead-in period (Day 1 to 7) →
Randomization (1:1:1:1) on Day 8 stratified by body weight gained during the olanzapine lead-in period (40 kg, >0 to <1 kg, or ≥1 kg) →
12-week, double-blind, olanzapine-controlled, treatment period (Week 1 to 12; Day 8 to 92) →
12-week, active treatment, dose-blinded, extension treatment period (Week 13 to 25; Day 92 to 176) →
4-week, safety, follow-up period (Week 25 to 29)
```

Source: 302 Clinical Study Report, Figure 1.

### 3.1.1.2. Results

The results from the 12-week randomized, controlled period of part A are presented below.

**Disposition**

A total of 347 subjects were enrolled; 38 (11%) of whom discontinued early from the 1-week olanzapine lead-in period. Therefore, 309 subjects were randomized to olanzapine plus placebo (n=75), olanzapine plus samidorphan 5 mg (n=80), olanzapine plus samidorphan 10 mg (n=86), and olanzapine plus samidorphan 20 mg (n=68). The proportions of subjects who discontinued early from the double-blind epoch of part A were 25%, 35%, 33%, and 19%, respectively.

**Demographics and Baseline Characteristics**

The majority of subjects in the FAS 1 efficacy population in this trial were male (74%), black or African American (61.3%), and residing in the United States (84%); 5.7% were of Hispanic or Latino ethnicity. Demographics were well-balanced among groups.

In the FAS 1 population, mean baseline BMI was 25.1 kg/m², and mean baseline weight was 76.3 kg. Mean values were similar among treatment groups.
Primary Efficacy Endpoint and Results

Treatment with olanzapine plus samidorphan was associated with similar change in symptoms as olanzapine plus placebo and was within the equivalence margin selected by the Applicant. Over the 12-week double-blind period, the LS mean change in PANSS total score in the pooled olanzapine plus samidorphan group was -2.2 (standard error=0.47). This finding was similar to the olanzapine plus placebo group, which had a change in PANSS score of -2.9 (SE=0.82). These changes were similar across all groups, and were supported by stable CGI-S scores, suggesting a flat dose-response for samidorphan.

Exploratory Results – Weight-Related Endpoints

Percent Weight Gain

In the FAS 1 population, the estimated difference in percent body weight between the olanzapine plus samidorphan group (all doses combined) and the olanzapine plus placebo group over the 12 weeks of the randomized trial was -1.5% (95% CI: -2.5, -0.4). A dose-dependent samidorphan effect was not observed in the FAS 1 population. However, in the FAS 2 population (those with early weight gain), there was some evidence of a dose-dependent response (see Table 3).

Table 3. Percent Change in Body Weight at Week 12 (Study 302, Part A; FAS 1 and FAS 2 Populations)

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>OLZ + PBO</th>
<th>OLZ + SAM 5mg</th>
<th>OLZ + SAM 10mg</th>
<th>OLZ + SAM 20mg</th>
<th>OLZ + All SAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS 1, n</td>
<td>74</td>
<td>75</td>
<td>83</td>
<td>67</td>
<td>225</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>76.0</td>
<td>78.3</td>
<td>77.4</td>
<td>75.8</td>
<td>77.2</td>
</tr>
<tr>
<td></td>
<td>(12.4)</td>
<td>(13.9)</td>
<td>(13.6)</td>
<td>(12.7)</td>
<td>(13.4)</td>
</tr>
<tr>
<td>% change at week 12, mean (SD)*</td>
<td>4.3</td>
<td>2.7</td>
<td>2.1</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>(7.1)</td>
<td>(5.0)</td>
<td>(5.7)</td>
<td>(6.0)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>% change at week 12, LS mean (SE)</td>
<td>4.1</td>
<td>2.8</td>
<td>2.1</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>(0.5)</td>
<td>(0.5)</td>
<td>(0.4)</td>
<td>(0.5)</td>
<td>(0.3)</td>
</tr>
<tr>
<td>95% CI of LS mean</td>
<td>3.2</td>
<td>5.0</td>
<td>3.7</td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td>(OLZ+SAM) – (OLZ+PBO), LS mean (SE)</td>
<td>-1.3</td>
<td>-1.9</td>
<td>-1.2</td>
<td>-1.5</td>
<td>-1.5</td>
</tr>
<tr>
<td></td>
<td>(0.7)</td>
<td>(0.6)</td>
<td>(0.7)</td>
<td>(0.5)</td>
<td>(0.5)</td>
</tr>
<tr>
<td>95% CI of LS mean difference</td>
<td>-2.6</td>
<td>0.0</td>
<td>-3.2</td>
<td>-0.7</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>-2.5</td>
<td>0.1</td>
<td>-0.4</td>
<td>-0.4</td>
</tr>
<tr>
<td>FAS 2, n</td>
<td>45</td>
<td>50</td>
<td>53</td>
<td>46</td>
<td>149</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>75.8</td>
<td>79.6</td>
<td>75.6</td>
<td>75.5</td>
<td>76.9</td>
</tr>
<tr>
<td></td>
<td>(13.3)</td>
<td>(14.2)</td>
<td>(12.7)</td>
<td>(13.1)</td>
<td>(13.4)</td>
</tr>
<tr>
<td>% change at week 12, mean (SD)</td>
<td>5.7</td>
<td>3.8</td>
<td>1.9</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>(7.5)</td>
<td>(4.5)</td>
<td>(5.7)</td>
<td>(4.6)</td>
<td>(5.0)</td>
</tr>
<tr>
<td>% change at week 12, LS mean (SE)</td>
<td>5.3</td>
<td>3.8</td>
<td>2.2</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>(0.6)</td>
<td>(0.6)</td>
<td>(0.6)</td>
<td>(0.6)</td>
<td>(0.3)</td>
</tr>
<tr>
<td>95% CI of LS mean</td>
<td>4.2</td>
<td>6.4</td>
<td>2.7</td>
<td>4.9</td>
<td>1.2</td>
</tr>
<tr>
<td>(OLZ+SAM) – (OLZ+PBO), LS mean (SE)</td>
<td>-1.4</td>
<td>-3.0</td>
<td>-3.7</td>
<td>-2.7</td>
<td>-2.7</td>
</tr>
<tr>
<td></td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.7)</td>
</tr>
<tr>
<td>95% CI of LS mean difference</td>
<td>-3.0</td>
<td>0.1</td>
<td>-4.6</td>
<td>-1.5</td>
<td>-5.3</td>
</tr>
<tr>
<td></td>
<td>-2.1</td>
<td>-4.0</td>
<td>-1.4</td>
<td>-4.0</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

Source: Reviewer generated based on 302 Clinical Study Report, Table 17.
*Week 12 = from randomization to the end of the 12-week double-blind phase

Abbreviations: CI = unadjusted confidence interval, FAS = full-analysis set, LS = least-squares, n = number of subjects in subgroup, OLZ = olanzapine, PBO = placebo, SAM = samidorphan, SD = standard deviation, SE = standard error
Figure 3 and Figure 4 show the trajectory of weight gain for the treatment arms over the 12-week period overall (Figure 3) and in the subpopulation of subjects with early weight gain (Figure 4). The olanzapine plus samidorphan arms appear to separate from olanzapine plus placebo after about day 36, particularly in the FAS 2 population.

**Figure 3. Percent Change in Body Weight by Treatment Group (Study 302, Part A, FAS 1)**

![Graph showing percent change in body weight by treatment group](source: 302 Clinical Study Report, Figure 7.)

Abbreviations: FAS = full-analysis set, LS = least-squares, OLZ = olanzapine, PBO = placebo, SAM = samidorphan, SE = standard error
In this trial, the Applicant used several cut-offs to define significant weight gain for the purposes of categorical analyses: ≥5%, ≥7% or ≥10% from baseline. Note that these analyses are conducted on completers and do not impute values for subjects with missing data. The proportion of completers with ≥10% weight gain was numerically smaller for the olanzapine plus samidorphan combined group versus the olanzapine plus placebo group.

Table 4. Categorical Weight Gain Assessment at Week 12 (Proportion of Completers Meeting Criteria: Study 302)

<table>
<thead>
<tr>
<th>Categories Assessed</th>
<th>OLZ + PBO</th>
<th>OLZ + SAM 5</th>
<th>OLZ + SAM 10</th>
<th>OLZ + SAM 20</th>
<th>OLZ + All SAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS 1, n</td>
<td>74</td>
<td>75</td>
<td>83</td>
<td>67</td>
<td>225</td>
</tr>
<tr>
<td>Completers, n</td>
<td>56</td>
<td>52</td>
<td>59</td>
<td>54</td>
<td>165</td>
</tr>
<tr>
<td>≥5% weight gain, n (%)</td>
<td>20 (36)</td>
<td>18 (35)</td>
<td>16 (27)</td>
<td>16 (30)</td>
<td>50 (30)</td>
</tr>
<tr>
<td>≥7% weight gain, n (%)</td>
<td>14 (25)</td>
<td>8 (15)</td>
<td>9 (15)</td>
<td>12 (22)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>≥10% weight gain, n (%)</td>
<td>10 (18)</td>
<td>3 (6)</td>
<td>4 (7)</td>
<td>5 (9)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>FAS 2, n</td>
<td>45</td>
<td>50</td>
<td>53</td>
<td>46</td>
<td>149</td>
</tr>
<tr>
<td>Completers, n</td>
<td>35</td>
<td>35</td>
<td>36</td>
<td>35</td>
<td>106</td>
</tr>
<tr>
<td>≥5% weight gain, n (%)</td>
<td>14 (40)</td>
<td>13 (37)</td>
<td>8 (22)</td>
<td>8 (23)</td>
<td>29 (27)</td>
</tr>
<tr>
<td>≥7% weight gain, n (%)</td>
<td>11 (31)</td>
<td>7 (20)</td>
<td>4 (11)</td>
<td>7 (20)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>≥10% weight gain, n (%)</td>
<td>8 (23)</td>
<td>3 (9)</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

Other Weight-Related Exploratory Endpoints

No notable differences between groups were observed for waist circumference in Study 302, Part A.
Metabolic and blood pressure parameters were considered safety endpoints in this trial and examined descriptively. Lipid and glycemic laboratory values were normal at baseline and changes over the 12-week randomized period generally did not occur in a dose-related fashion. Potentially adverse findings observed with samidorphan include dose-related increases in fasting glucose (at any postbaseline visit, 16% of subjects on olanzapine plus placebo, 17% of subjects on olanzapine plus samidorphan 5 mg, 32% of subjects on olanzapine plus samidorphan 10 mg, and 32% of subjects on olanzapine plus samidorphan 20 mg reported increases in fasting glucose of at least 10 mg/dL).

Mean supine systolic and diastolic blood pressure values were within normal limits at baseline; changes over the 12-week randomized period were small and likely clinically insignificant.

3.1.2. Study ALK3831-A303

This was a phase 3, multicenter (U.S. sites only), olanzapine-controlled, randomized, double-blind study in adults with schizophrenia designed to assess the effect of samidorphan 10 mg on olanzapine-associated weight gain over the 24-week study duration. Reviewers from the Division of Diabetes, Lipids, and Obesity (DDLO) were involved in meetings with the Applicant regarding this pivotal trial and relevant study endpoints.

3.1.2.1. Trial Design

This study was a randomized, double-blind, multicenter, parallel-group, active-controlled design comparing doses of ALKS 3831 (10/10 mg daily titrated to 20/10 mg daily) to olanzapine (10 mg daily titrated to 20 mg daily) over a 24-week treatment period. The subjects were ages 18 years to 55 years who were diagnosed with schizophrenia.

Figure 5. Schematic of Study A303

Source: A303 Clinical Study Report, Figure 1.

Dosing

One dose of study drug was to be administered daily, preferably at bedtime. Subjects were to receive ALKS 3831 (10 mg/10 mg) or olanzapine 10 mg daily from Visit 2, then titrated to ALKS 3831 (20 mg/10 mg) or olanzapine 20 mg daily at the end of Week 1. If the titrated dose
was not tolerated, the dose could be decreased back to ALKS 3831 (10 mg/10 mg) or olanzapine 10 mg at the end of Week 2, Week 3, or Week 4; no dose changes were permitted beyond Week 4. Doses were selected based on approved olanzapine doses and data from Study 302.

**Study Schedule**

Study visits occurred at screening, weekly through Week 6, then every other week through Week 28.

**Study Endpoints**

The Study’s co-primary endpoints were (1) weight change from baseline, and (2) a categorical/responder analysis of proportion of subjects in each group with a clinically relevant change in weight from baseline. The key secondary endpoint was the proportion of subjects who gained 7% or more weight from baseline to Week 24.

**Statistical Considerations**

The primary analysis results for the first co-primary endpoint were obtained by analysis of covariance with baseline weight as a covariate and the factors of treatment group, age group, and race. Post-baseline missing values were handled by the multiple imputation method.

The primary analysis result for the second co-primary endpoint was obtained with a logistic regression model with baseline weight as a covariate and the factors of treatment group, age group, and race. Post-baseline missing values were handled by the multiple imputation method. The Applicant estimated treatment effects in terms of the odds ratio (primary measure) and difference in proportion between the two groups (supportive measure) for the second co-primary endpoint, the proportion of subjects who gained 10% or more weight from their baseline.

The key secondary endpoint (proportion of subjects who gained 7% or more of their baseline weight) was analyzed using the same method as for the second co-primary endpoint, as described above.

The Applicant pre-specified an unblinded interim analysis with a conditional power approach for a possible increase in sample size. A sample size increase, without any adjustment, may inflate the overall type I error rate in a statistical test. To control the overall type I error rate due to the sample size increase, the Cui, Hung, and Wang (CHW) (Cui et al. 1999) test statistic was pre-specified to derive the p-values from the primary testing of each co-primary endpoint. However, for all others (such as sensitivity analyses of the co-primary endpoints, analyses for secondary efficacy endpoints), the unadjusted test statistic (that is, without considering sample size increase) was pre-specified to derive the p-values. Treatment effect estimates (in terms of point estimate and confidence interval) for all efficacy endpoints, including co-primary endpoints, were derived without adjusting for sample size increase.

**3.1.2.2. Results**

Based on pre-specified criteria, the Applicant increased the initially targeted sample size of 400 (200 per arm) to 540 (270 per arm). As the results were very similar regardless of whether or not an adjustment for sample size increase is made, the reporting in this document will be based on the unadjusted approach, unless noted.
**Disposition**

A total of 561 subjects were randomized: 280 to ALKS 3831 and 281 to olanzapine. The safety population consisted of 550 subjects who received at least one dose of study drug. The FAS Population (efficacy population) consisted of 538 subjects who had at least one postbaseline weight assessment.

A total of 352 subjects (64%) completed the study; 36% of subjects discontinued in both the ALKS 3831 and the olanzapine arms. Reasons for discontinuation included adverse events (11%), subject withdrawal (9%), and loss to follow-up (9%). The incidence of discontinuation due to adverse events (AEs) was slightly higher in the ALKS 3831 group (12%) compared to the olanzapine group (10%).

**Demographics and Baseline Characteristics**

Most subjects in the trial were male (73%), black or African-American (71%), and not of Hispanic ethnicity (86%). Mean age was 40 years, with a range (by trial design) of 18 years to 55 years. The majority of subjects in the trial (56%) were overweight (BMI ≥25 kg/m²), with a mean BMI of 25.4 kg/m² and a mean weight of 77.2 kg. Demographic and baseline characteristics were well-balanced among groups.

**First Coprimary Endpoint: Percent Change from Baseline in Weight at Week 24**

The mean percent change from baseline in weight was significantly lower in patients treated with ALKS 3831 than in patients treated with olanzapine (CHW test; p = 0.003). As shown in Table 5, the treatment effect estimate (difference in mean percent weight change from baseline between ALKS 3831 and olanzapine) was -2.38% (95% CI: -3.88%, -0.88%), favoring ALKS 3831.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Subjects</th>
<th>Mean Baseline Weight (SD, kg)</th>
<th>Percent Change From Baseline in Weight</th>
<th>Treatment Difference (ALKS 3831 – Olanzapine) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKS 3831</td>
<td>266</td>
<td>77.0 (13.7)</td>
<td>4.2 (0.7)</td>
<td>-2.38</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>272</td>
<td>77.5 (13.5)</td>
<td>6.6 (0.67)</td>
<td>(-3.88, -0.88)</td>
</tr>
</tbody>
</table>

Source: Based on A303 Clinical Study Report, Table 11, confirmed by FDA statistical reviewer.
P-value from the unadjusted test statistic was 0.002
Abbreviations: CI = unadjusted confidence interval, LS = least-squares, SD = standard deviation, SE = standard error.

**Figure 6** displays the LS mean percent weight gain from baseline over time. It suggests that the weight mitigation of ALK3831 versus olanzapine is first observed at approximately 6 weeks of treatment.
Figure 6. LS Mean Percent Change Weight Gain from Baseline by Treatment During 24-Week Double-Blind Period (Study A303)

LS Mean Percent Change from Baseline in Body Weight by Visit (ANCOVA)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ALKS3831</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects observed</td>
<td>ALKS 3831</td>
<td>265</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>266</td>
<td>265</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer.
Note: LS Mean is based on Primary Analysis Model ANCOVA at each visit, not that data from all visits were included in one model. Abbreviations: ANCOVA = analysis of covariance, LS = least-squares, SE = standard error.

Second Coprimary Endpoint: Proportion of Subjects Who Had ≥10% Increase in Weight from Baseline to Week 24

The proportion of patients who had gained 10% or more weight from baseline to Week 24 was significantly lower in subjects treated with ALKS 3831 than in subjects treated with olanzapine (CHW test; p = 0.003).

As shown in Table 6, the odds ratio (ALKS3831/olanzapine) for having a 10% or greater increase in weight from baseline to Week 24 was 0.50 (95% CI: 0.31, 0.80). The proportion of patients who gained 10% or more weight from their baseline was significantly lower for ALKS 3831 (17.8%) than for olanzapine (29.9%), with an absolute 13.7% difference between the groups (95% CI: -22.8%, -4.6%).
Table 6. Primary Analysis for Second Coprimary Endpoint (Study A303)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Subjects</th>
<th>Number* (Percent) Subjects With ≥10% Increase</th>
<th>Primary Measure Odds Ratio (ALKS 3831/Olanzapine) (95% CI)</th>
<th>Supportive Measure Difference in Relative Risk (ALKS 3831 – Olanzapine) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKS 3831</td>
<td>266</td>
<td>47 (17.8)</td>
<td>0.50 (0.31, 0.80)</td>
<td>-13.7 (-22.8, -4.6)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>272</td>
<td>81 (29.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Based on A303 Clinical Study Report, Table 14.2.3, confirmed by FDA statistical reviewer.
* Number of responders and proportion are the mean number of responders and mean proportion from 500 imputed datasets, respectively. The mean number of responders is rounded up to the nearest integer. The p-value from the unadjusted test statistic was 0.004.

Abbreviations: CI = unadjusted confidence interval, LS = least-squares, SD = standard deviation, SE = standard error.

Key Secondary Endpoint: Proportion of Subjects Who Had ≥7% Increase in Weight from Baseline to Week 24

The proportion of patients who had gained 7% or more weight from baseline to Week 24 was significantly lower in subjects treated with ALKS 3831 than in subjects treated with olanzapine (p = 0.001, unadjusted for sample size increase).

As shown in **Table 7**, the odds ratio (ALKS 3831/olanzapine) for having a 7% or greater increase in weight from baseline to Week 24 was 0.50 (95% CI: 0.33, 0.76). The proportion of patients who gained 7% or more weight from their baseline was significantly lower for ALKS 3831 (27.5%) than for olanzapine (42.7%), with an absolute 15.9% difference between the groups (95% CI: -22.8, -4.6%).

Table 7. Primary Analysis Results for Key Secondary Endpoint (Study A303)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Subjects</th>
<th>Number* (Percent) of Subjects With ≥7% Weight</th>
<th>Primary Measure Odds Ratio (ALKS 3831/Olanzapine) (95% CI)</th>
<th>Supportive Measure Difference in Relative Risk (ALKS 3831 – Olanzapine) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKS 3831</td>
<td>266</td>
<td>73 (27.5)</td>
<td>0.50 (0.33, 0.76)</td>
<td>-15.9 (-25.3, -6.5)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>272</td>
<td>116 (42.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Based on A303 Clinical Study Report, Table 14.2.7, confirmed by FDA statistical reviewer.
* Number of responders and proportion are the mean number of responders and mean proportion from 500 imputed datasets, respectively. The mean number of responders is rounded to the nearest integer.

Abbreviations: CI = unadjusted confidence interval, LS = least-squares, SD = standard deviation, SE = standard error.

A cumulative frequency distribution plot shows a left shift of the curve in the ALKS 3831 group across proportions in week 24 weight change (**Figure 7**).
Premature Discontinuations and Missing Data

The primary multiple imputation analysis relied on the missing at random assumption, suggesting that all observed response trajectories can be used to estimate the unobserved outcomes. Specifically, the missing data were imputed sequentially by each visit using a regression method. The imputation regression model included treatment group, race, and baseline age as factors, and body weight at all previous visits (including baseline weight) as covariates.

In Study A303, 186 subjects (34.6%) from the efficacy population discontinued their assigned study drug before the Week 24 weight assessment. Discontinuations were similar across treatment groups. Weight increase was not identified as a reason for a discontinuation from the assigned treatment for most of the subjects who dropped out; a relatively small proportion of subjects prematurely discontinued study drug due to an adverse event of “weight increased” during the double-blind period (four subjects (1.5%) on ALKS 3831 and two (0.7%) on olanzapine).
It is unclear if the proportion of subjects who discontinued drug in this trial reflects what would occur in clinical practice. For example, body weight changes poststudy discontinuation could reflect, in part, the antipsychotic drug(s) the subjects begin when they stop an olanzapine-based therapy. (Risperidone and quetiapine were the most frequently used antipsychotics in the subjects who prematurely discontinued, and their use was generally similar among randomized groups. Both drugs have modest weight gain in comparison to olanzapine, see Figure 1.)

Sensitivity Analyses

Although the appropriateness of the primary analysis strategy with use of multiple imputation under a missing at random assumption cannot be verified or proven to be correct, sensitivity analyses inform the robustness of the primary efficacy analysis result.

The Applicant performed several prespecified sensitivity analyses:

- The first prespecified sensitivity analysis was based on the delta-adjusted pattern mixture model (see Table 8). Like in the primary analysis, missing data were imputed sequentially by each visit using a regression model. The model imputed the weight gain for subjects prematurely discontinuing from the olanzapine group to be diminished (that is, to be imputed with better weight outcomes) by a set percentage of the observed treatment difference (in percent weight gain) between the two treatment groups (-2.38% from the primary analysis). It progressively increased this percentage in increments, imputing the weight closer and closer to the ALKS 3831 group, to identify the tipping point at which there was no longer a statistical significance between treatment groups. The results showed that even when the olanzapine-treated subjects who discontinued would have, on average, their unobserved percent weight gain decreased by 80% of the observed treatment difference from the primary analysis (that is, decreased by 2.38*80% = 1.9%), we would still see a statistically significant difference at week 24, with an estimated treatment difference in weight gain of -1.51% (95% CI: -3.00, -0.01). Although the result would still be statistically significant, it is uncertain whether this magnitude of effect is clinically relevant. On the other hand, this is a very conservative estimate because it assumes that the olanzapine-treated subjects who dropped out would have, on average, considerably better outcomes if they had not dropped out than the olanzapine-treated subjects who continued treatment.

Table 8. Sensitivity Analysis of Percent Change from Baseline in Body Weight at Week 24 – Delta Adjusted Pattern Mixture Model (Study A303)

<table>
<thead>
<tr>
<th>Category Statistic</th>
<th>Shift Parameter</th>
<th>ALKS 3831</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>LS mean difference (SE) vs. olanzapine</td>
<td>-</td>
<td>-2.38 (0.77)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>70% of treatment difference between ALKS 3831 and olanzapine (%)</td>
<td>-1.66</td>
<td>-</td>
</tr>
<tr>
<td>LS mean difference (SE) vs. olanzapine</td>
<td>-</td>
<td>-1.61 (0.76)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>80% of Treatment Difference between ALKS 3831 and olanzapine (%)</td>
<td>-1.90</td>
<td>-</td>
</tr>
<tr>
<td>LS mean difference (SE) vs. olanzapine</td>
<td>-</td>
<td>-1.51 (0.76)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.048</td>
</tr>
<tr>
<td>Category Statistic</td>
<td>Shift Parameter</td>
<td>ALKS 3831</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>90% of treatment difference between ALKS 3831 and olanzapine (%)</td>
<td>-2.14</td>
<td>—</td>
</tr>
<tr>
<td>LS mean difference (SE) vs. olanzapine</td>
<td>—</td>
<td>-1.41 (0.76)</td>
</tr>
<tr>
<td>p-value</td>
<td>—</td>
<td>0.066</td>
</tr>
<tr>
<td>100% of treatment difference between ALKS 3831 and olanzapine (%)</td>
<td>-2.38</td>
<td>—</td>
</tr>
<tr>
<td>LS mean difference (SE) vs. olanzapine</td>
<td>—</td>
<td>-1.31 (0.77)</td>
</tr>
<tr>
<td>p-value</td>
<td>—</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Source: Based on A303 Clinical Study Report, Tables 11 and Table 13, confirmed by FDA statistical reviewer.

* Estimates and p-values were unadjusted for the sample size increase. The delta adjusted pattern mixture model is implemented using multiple imputation with 500 imputations to incorporate the assumption of missing-not-at-random.

* Olanzapine subjects who discontinue would have, on average, their unobserved percent weight gain decreased by the shift parameter compared with the observed weight gain of olanzapine subjects who continue.

* The shift parameters account for up to 100% of the observed treatment difference between olanzapine and ALKS 3831 from the primary analysis of the percent change from baseline in body weight at week 24 in the FAS Population.

* ALKS 3831 subjects who discontinue would have the same weight gain trajectory as the ALKS 3831 subjects that stay on the study. The ANCOVA model is used to analyze the change from baseline at week 24. Rubin’s rule is used to combine the treatment effect estimates and standard errors across imputations.

Abbreviations: CI = unadjusted confidence interval, LS = least squares, SE = standard error, ANCOVA = analysis of covariance

- The Applicant performed a second prespecified sensitivity analysis by repeating the primary analysis but including both on- and off-treatment weight assessments after premature discontinuation of study drug. Forty of the 186 early discontinuing subjects had off-treatment weight assessments at Week 24 (18 and 22 subjects for the ALKS 3831 and olanzapine groups, respectively). Sixty-eight early discontinuing subjects returned for off-treatment interval weight assessments, but not for the Week 24 assessment. Figure 8 displays the mean weight gain trajectories for the completers’ cohort and noncompleters’ cohorts, composed of those who discontinued at the same visit. Whereas the top panel summarizes on-treatment weights only, the bottom panel incorporates these discontinued subjects with off-treatment weights. The curves of the weight assessments for subjects randomized to olanzapine are generally higher than those randomized to ALKS 3831, regardless of whether they are on- or off-treatment assessments. Weight gain in both treatment groups was slightly attenuated in this analysis compared with the primary analysis. The difference between the treatment groups (ALKS 3831 – olanzapine) was similar to the primary analysis (Table 5). The response trajectories including off-treatment assessments did not differ much from the trajectories without off-treatment assessments—possibly because only 40 of the 168 discontinuing subjects were added in as “completers” and there were still many missing data in describing the response trajectories. The slightly attenuated percent weight gain observed in the olanzapine response trajectories that incorporated off-treatment assessments also suggests that the resulting estimated treatment difference of -1.51% (95% CI: -3.00, -0.01) in the first sensitivity analysis (via a delta-adjusted pattern mixture model) may be very conservative. This is because it was derived based on the assumption that the unobserved percent weight gain in olanzapine dropouts had been, on average, relatively smaller than the olanzapine subjects who continued treatment, with a difference of 1.9% (=2.38*80%, where 2.38% is the point estimate of treatment difference from the primary analysis) between olanzapine-treated subjects who dropped out and those who did not.
Figure 8. Mean Weight Trajectories of Subjects in Various Cohorts (Study A303)

Source: Applicant’s response to May 7, 2020, Agency Request for Information, Figure 5 (eCTD 0006).

Performed on the primary efficacy analysis set.

The top panels present the on-treatment weight results. The orange line denotes the mean weight gain curve of completers with on-treatment weight assessments at week 24. Other lines denote the mean weight gain of all subjects with their last on-treatment weight assessment at a given visit.

The bottom panels present the on- and off-treatment weight results. The orange line denotes the mean weight gain curve of subjects with weight assessments at week 24 (including both completers and retrieved dropouts). Other lines denote the mean weight gain of subjects who have their last weight assessments (including on- and off-treatment results) at a given visit.

Numbers of subjects included in each curve are noted.
Table 9. Sensitivity Analyses by Including Both On- and Off-Treatment Weight Assessments after Premature Discontinuation of Study Drug (Study A303)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>First Coprimary Endpoint: Percent Change from Baseline in Body Weight at Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity Analysis (Including Both On-Treatment and Off-Treatment Weight Assessments)</td>
</tr>
<tr>
<td></td>
<td>Treatment Difference (ALKS 3831 – Olanzapine) (95% CI)</td>
</tr>
<tr>
<td>ALKS 3831</td>
<td>3.89 (0.84)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>6.29 (0.63)</td>
</tr>
</tbody>
</table>

Source: based on A303 Clinical Study Report, Tables 14.2.1 and 14.2.2.3.2, confirmed by FDA statistical reviewer.
Abbreviations: CI = unadjusted confidence interval, LS = least-squares, SD = standard deviation, SE = standard error.

- The Applicant performed a third prespecified sensitivity analysis using a mixed-effect model with repeated measures. The results were similar to those of the primary analysis. LS mean weight change in this analysis was 3.78% in the ALKS 3831 group and 6.10% in the olanzapine group. The difference between groups was -2.32% (95% CI: -3.79, -0.85).

The Applicant also performed the same sensitivity analyses on the second coprimary endpoint (proportion of subjects with ≥10% in weight gain at Week 24). The results support the robustness of the primary analysis on this categorical coprimary endpoint. In particular, even when the unobserved percent weight gain for olanzapine-treated subjects who discontinued is assumed to be, on average, 2.38% (that is, 100% of the estimated treatment difference from the primary analysis) smaller than olanzapine subjects who continued, the results are still statistically significant in favor of ALKS 3831, with an odds ratio estimate of 0.58 (95% CI: 0.36, 0.92). Analysis by adding in off-treatment assessments resulted in an odds ratio estimate of 0.46 (95% CI: 0.29, 0.74).

Upon FDA request, additional sensitivity analyses were conducted for the categorical coprimary endpoint (proportions of subjects with ≥10% in body weight from baseline to Week 24), in which subjects with missing weight assessments at Week 24 are imputed as (1) gaining ≥10% in body weight from baseline at Week 24, and (2) not gaining that amount of weight (<10%) at Week 24. As seen in Table 10, imputing missing values as ≥10% weight gain or <10% weight gain results in some attenuation of the treatment effect, both as measured by odds ratio and risk difference.
Table 10. Additional Analyses for Proportion of Subjects With ≥10% Weight Gain from Baseline at Week 24 by Imputation Method (Study A303)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Imputation Method for Missing Data</th>
<th>ALKS 3831 N=266</th>
<th>OLZ N=272</th>
<th>ALKS 3831 vs. OLZ Odds Ratio (95% CI)</th>
<th>ALKS 3831 vs. OLZ Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10% weight gain at week 24</td>
<td>Primary analysis (MI for missing data)</td>
<td>47 (17.8) n (%)</td>
<td>81 (29.8) n (%)</td>
<td>0.50 (0.31, 0.80)</td>
<td>-13.7 (-22.8, -4.6)</td>
</tr>
<tr>
<td></td>
<td>Impute missing as ≥ 10% weight gain</td>
<td>119 (44.7) n (%)</td>
<td>146 (53.7) n (%)</td>
<td>0.69 (0.49, 0.98)</td>
<td>-8.9 (-17.4, -0.5)</td>
</tr>
<tr>
<td></td>
<td>Impute missing as &lt;10% weight gain</td>
<td>30 (11.3) n (%)</td>
<td>49 (18.0) n (%)</td>
<td>0.57 (0.35, 0.93)</td>
<td>-6.7 (-12.7, -0.8)</td>
</tr>
</tbody>
</table>

Source: Applicant’s Response to May 7, 2020, Agency Request for Information, Tables Q2.1 and Q2.2.
Abbreviations: CI = unadjusted confidence interval, MI = multiple imputation, OLZ = olanzapine.

It is also possible that the olanzapine dropouts would have, on average, had much larger percent weight gains, had they not dropped out, in which case the estimated treatment effect would likely be larger than that of the primary analysis. The uncertainty lies in whether the unobserved outcomes can be reasonably estimated based on the observed response trajectories.

Overall, the sensitivity analyses support the robustness of the primary analysis results to deviation from the missing data assumption imposed for the primary analysis.

**Supportive Metabolic Endpoints**

Aside from waist circumference, for which the magnitude of the treatment difference is consistent with the mean weight change, no meaningful difference in metabolic endpoints was observed between ALKS 3831 and olanzapine (see Table 11).

Table 11. Other Secondary Metabolic Endpoints, Week 24 (Study A303)

<table>
<thead>
<tr>
<th>Metabolic Endpoints</th>
<th>ALKS 3831 N=266</th>
<th>OLZ N=272</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>90.75 (10.885)</td>
<td>90.92 (10.611)</td>
</tr>
<tr>
<td>Mean (SD) week 24</td>
<td>92.74 (11.259)</td>
<td>95.03 (11.780)</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>2.36 (1.26, 3.46)</td>
<td>4.47 (3.40, 5.54)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>-2.12 (-3.35, -0.89)</td>
<td></td>
</tr>
<tr>
<td>Fasting total cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>285</td>
<td>270</td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>183.4 (34.74)</td>
<td>185.2 (37.27)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>162</td>
<td>166</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>0.66 (-3.400, 4.710)</td>
<td>2.48 (-1.500, 6.453)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>-1.82 (-7.12, 3.48)</td>
<td></td>
</tr>
<tr>
<td>Fasting HDL cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>285</td>
<td>270</td>
</tr>
<tr>
<td>Mean (SD) Baseline</td>
<td>62.4 (22.42)</td>
<td>62.1 (21.02)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>162</td>
<td>166</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>-6.16 (-8.015, -4.313)</td>
<td>-5.74 (-7.562, -3.925)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>-0.42 (-2.85, 2.01)</td>
<td></td>
</tr>
<tr>
<td>Metabolic Endpoints</td>
<td>ALKS 3831 N=266</td>
<td>OLZ N=272</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Fasting LDL cholesterol, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>264</td>
<td>270</td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>109.6 (32.26)</td>
<td>112.7 (33.98)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>161</td>
<td>166</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>0.52 (-3.281, 4.316)</td>
<td>1.53 (-2.188, 5.257)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>-1.02 (-6.01, 3.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Fasting triglycerides, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>265</td>
<td>270</td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>114.4 (93.96)</td>
<td>107.1 (62.14)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>162</td>
<td>166</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>26.77 (15.408, 38.136)</td>
<td>29.36 (18.183, 40.532)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>-2.58 (-17.59, 12.42)</td>
<td></td>
</tr>
<tr>
<td><strong>Fasting glucose, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>265</td>
<td>270</td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>90.3 (11.60)</td>
<td>91.4 (12.03)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>160</td>
<td>166</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>3.83 (1.69, 5.97)</td>
<td>2.34 (0.25, 4.43)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>1.49 (-1.33, 4.30)</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>266</td>
<td>272</td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>5.40 (0.377)</td>
<td>5.40 (0.420)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>173</td>
<td>173</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>0.05 (0.01, 0.09)</td>
<td>0.06 (0.02, 0.10)</td>
</tr>
<tr>
<td>LS mean difference ALKS 3831 – OLZ (95% CI)</td>
<td>-0.01 (-0.06, 0.05)</td>
<td></td>
</tr>
<tr>
<td><strong>Fasting Insulin, µIU/mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>265</td>
<td>269</td>
</tr>
<tr>
<td>Mean (SD) baseline</td>
<td>12.65 (20.868)</td>
<td>12.12 (15.848)</td>
</tr>
<tr>
<td>Week 24, n</td>
<td>162</td>
<td>161</td>
</tr>
<tr>
<td>LS mean (95% CI) change</td>
<td>3.38 (-0.18, 6.94)</td>
<td>4.07 (0.51, 7.63)</td>
</tr>
<tr>
<td>LS mean difference in change from baseline</td>
<td>-0.68 (-5.54, 4.18)</td>
<td></td>
</tr>
</tbody>
</table>

Source: A303 Clinical Study Report, Table 14.2.16 (waist circumference), Table 16 (lipids), Tables 17 and 14.2.14.1 (glycemic parameters)

*a analyzed with MI ANCOVA

*b analyzed with mixed-effect model repeated measure (observed data)

Abbreviations: CI = unadjusted confidence interval, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LS = least-squares, n = number of subjects in subgroup, SD = standard deviation, SE = standard error, ANCOVA = analysis of covariance

In subjects treated with ALKS 3831, there was a trend of increased fasting glucose as compared to olanzapine (Figure 9). There were no notable changes in HbA1c and there were no differences in fasting insulin between groups. Fasting insulin can be considered a proxy for insulin resistance in subjects without diabetes mellitus, as fasting insulin rises as subjects become more insulin resistant (Quon 2001).
The clinical significance of the observed mean changes in fasting glucose is unclear in a population without diabetes mellitus, where the intent of the drug is to mitigate adverse alterations in metabolic parameters in patients treated with olanzapine. Nevertheless, a fuller picture of the impact of ALKS 3831 on fasting glucose is presented in Table 12, Figure 10, and Figure 11, which show proportions of subjects with categorical increases in glucose over time.

### Table 12. Categorical Increases in Glucose and HbA1c (Study A3030)

<table>
<thead>
<tr>
<th>Potentially Clinically Significant Criterion</th>
<th>ALKS 3831 n=274</th>
<th>Olanzapine n=276</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose, fasting (≥126 mg/dL)</strong>, proportion (%)</td>
<td>35/261 (13)</td>
<td>23/266 (9)</td>
</tr>
<tr>
<td><strong>Serum glucose (fasting) mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;100) to high (≥126), proportion (%)</td>
<td>26/223 (12)</td>
<td>18/219 (8)</td>
</tr>
<tr>
<td>Normal/impaired (&lt;126) to high (≥126), proportion (%)</td>
<td>35/261 (13)</td>
<td>23/266 (9)</td>
</tr>
<tr>
<td>Increase ≥10 mg/dL, proportion (%)</td>
<td>174/265 (66)</td>
<td>154/270 (57)</td>
</tr>
<tr>
<td><strong>HbA1c %, shift from baseline (&lt;5.7%) to:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postbaseline ≥5.7%, proportion (%)</td>
<td>87/204 (43)</td>
<td>71/197 (36)</td>
</tr>
<tr>
<td>Postbaseline ≥6.5%, proportion (%)</td>
<td>1/204 (0.5)</td>
<td>3/197 (2)</td>
</tr>
</tbody>
</table>

Source: Reviewer-generated from the A303 Clinical Study Report, Tables 49 and 51. Abbreviations: HbA1c = hemoglobin A1c, n = number of subjects in subgroup.
Figure 10. Proportion of Subjects with Baseline Fasting Glucose < 126 mg/dL and a Subsequent Fasting Glucose ≥ 126 mg/dL (Study A303)

PCS = Potentially clinically significant; “Sustained” = subjects with two consecutive PCS outcomes at the last two visits culminating in week 24.
Source: FDA Statistical Reviewer.
Overall, the glucose and insulin concentrations and related adverse events were mixed in this trial, with no meaningful difference between ALKS 3831 and olanzapine. While there is no obvious mitigation of the effect of olanzapine on fasting glucose with samidorphan based on these data, it is unclear what the impact of weight mitigation on glycemic parameters would be long-term.

As noted above, in general, mean lipid changes were similar between groups, with an apparent small attenuation of the rise in triglycerides (TG) with ALKS 3831 at any time Figure 12.
Figure 12. Proportion of Subjects with Baseline Triglycerides <200 and a Subsequent Triglyceride Measurement of ≥ 200 mg/dL (A303)

![Graph showing proportion of subjects with triglycerides at different times and treatment groups.]

PCS = Potentially clinically significant; "Sustained" = subjects with two consecutive PCS outcomes at the last two visits culminating in week 24.
Source: FDA Statistical Reviewer.

**Blood Pressure**

Vital signs were collected as safety endpoints, but changes in blood pressure (BP) could be relevant for interpreting the clinical significance of weight differences between treatment groups. Olanzapine is not labeled for increases in blood pressure, although orthostatic hypotension is described.

Changes from baseline in BP are shown in the safety population (Table 13).

**Table 13. Blood Pressure (Study A303)**

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>ALKS 3831 (N=274)</th>
<th>Olanzapine (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline (SD)</td>
<td>121.6 (12.88)</td>
<td>121.8 (11.90)</td>
</tr>
<tr>
<td>Mean change from baseline (SD)</td>
<td>-0.4 (10.82)</td>
<td>2.3 (12.57)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline (SD)</td>
<td>77.4 (9.37)</td>
<td>77.3 (9.70)</td>
</tr>
<tr>
<td>Mean change from baseline (SD)</td>
<td>0.7 (8.32)</td>
<td>1.6 (9.71)</td>
</tr>
</tbody>
</table>

Source: A303 Clinical Study Report, Table 56.
Abbreviations: N = number of subjects, OLZ = olanzapine, SD = standard deviation
The Applicant reported in a post hoc analysis that the LS mean difference (ALKS 3831 – olanzapine) in systolic and diastolic BP in mmHg at Week 24 was -2.60 (95% CI -4.73, -0.47) and -0.70 (-2.23, 0.84), respectively. In addition, Figure 13 suggests that the separation between groups in systolic BP was seen by Week 4 and persisted across the double-blind treatment period.

**Figure 13. Change from Baseline in Blood Pressure by Visit (Study A303)**

**Systolic**

**Diastolic**

Source: Response to May 7, 2020, Agency Request for Information, Figure 4.
Based on mixed model with repeated measurements (MMRM) using observed data
Note: The numbers under the figure indicate the number of patients at each timepoint
Abbreviations: LS = least squares, SE = standard error
Although increases of ~2 mmHg in systolic BP can increase risk for stroke, heart attack, and death in subjects with existing high blood pressure per the draft guidance for industry, *Assessment of Pressor Effects of Drugs (May 2018)*, the outcomes of decreases of this magnitude are less certain in subjects who are normotensive. Although this relatively small-magnitude difference may be a spurious finding, preventing even small increases in BP over many years is likely to be favorable for cardiovascular health.

3.1.3. Study ALK3831-A305

Study A305 was a phase 3, multinational (including U.S. sites), placebo- and active-controlled, randomized, double-blind study designed to assess ALKS 3831 as a treatment for the acute exacerbation of schizophrenia. Subjects began the study as inpatients for 4 weeks.

3.1.3.1. Trial Design

This study was a randomized, double-blind, multicenter, parallel-group, placebo-controlled inpatient design comparing ALKS 3831 (at 10 mg/10 mg daily or 20 mg/10 mg daily) to placebo after a 4-week treatment period. Olanzapine (10 mg daily or 20 mg daily) was included to explore its comparability with ALKS 3831. The subjects were ages 18 years to 70 years who were diagnosed with schizophrenia and experiencing an acute exacerbation.

**Figure 14. Schematic of Study A305**

![Schematic of Study A305](source: A305 Clinical Study Report, Figure 1. Abbreviations: EOT = end of treatment, OLZ = olanzapine)

**Dosing**

One dose of study drug was to be administered daily, preferably at bedtime. Subjects in the active treatment arms were to receive ALKS 3831 (10 mg/10 mg) or olanzapine 10 mg daily for day 1 and day 2, then ALKS 3831 (20 mg/10 mg) or olanzapine 20 mg daily thereafter. If the titrated dose was not tolerated, the dose could be decreased back to ALKS 3831 (10 mg/10 mg)
or olanzapine 10 mg at the end of week 1 or week 2; no other dose changes were permitted during the study. The doses were selected based on approved olanzapine doses and study data from study ALK3831-302.

**Study Schedule**

On the day of screening, subjects were admitted to an inpatient study facility for 2 weeks; subjects were discharged starting at week 2, if meeting discharge criteria. Subjects who were discharged at week 2 or week 3 were contacted once between weekly outpatient visits. Subjects who were inpatient at the end of 4 weeks of treatment could enroll in the extension study or remain inpatient for an additional week. Subjects who did not enroll in the extension study entered a 2-week safety follow-up period.

**Study Endpoints**

The primary efficacy endpoint was the PANSS total score. The primary analysis was based on a mixed model with repeated measurements with an unstructured variance-covariance matrix. The model included region (U.S. versus non-U.S.), visit, treatment, and interaction term of visit and treatment as categorical variables, and baseline PANSS total score as a covariate. All observations in the efficacy population data will be included in the analysis. Missing data were not imputed.

### 3.1.3.2. Results

**Disposition**

A total of 403 subjects were randomized: 134 to ALKS 3831, 134 to olanzapine, and 135 to placebo. Of those, 401 subjects were included in the safety population, and 397 subjects were included in the efficacy population.

Overall, 87.8% (352/401) subjects completed the study, and 12.2% of subjects discontinued from the double-blind period. Overall, the major discontinuation reason was **withdrawal by subjects** (6.2%), followed by **adverse event** (2.7%) and **lack of efficacy** (2.7%). Withdrawal rates were similar by treatment arm.

**Demographics and Baseline Characteristics**

In this trial, 69% of subjects were White, and 28% were Black or African-American. The mean age was 41 years (range: 18 years to 67 years), and 61% of the subjects were males. The mean (median) BMI was 26.6 (25.6) kg/m². The majority of subjects were in normal BMI range (18.5 kg/m² to <25 kg/m²). A total of 38.4% of the subjects were from the United States. All other subjects were from Bulgaria, Ukraine, or Serbia. The mean baseline PANSS total scores were similar across treatment groups.

**Efficacy Results – Primary Endpoint**

Treatment with ALKS 3831 was associated with improvement in schizophrenia symptoms. The LS mean change from baseline in PANSS total score was -17.5 in the placebo group, -23.9 in the ALKS 3831 group, and -22.8 in the olanzapine group; LS mean difference between ALKS 3831 and placebo treatment was -6.4 (95% CI: -10.2, -2.8) (Table 14). These primary findings were
corroborated by the result of the secondary efficacy endpoint CGI-S change from baseline. Although no formal noninferiority testing was conducted, the improvement in schizophrenia symptoms appeared similar between ALKS 3831 and olanzapine.

Table 14. Change from Baseline in PANSS Total Score at Week 4 (Study A305)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Subjects</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKS 3831</td>
<td>132</td>
<td>101.8 (11.61)</td>
<td>-23.9 (1.28)</td>
<td>-6.4 (-10.0, -2.8)*</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>132</td>
<td>100.6 (12.09)</td>
<td>-22.8 (1.29)</td>
<td>-5.3 (-8.9, -1.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>133</td>
<td>102.7 (11.85)</td>
<td>-17.5 (1.32)</td>
<td>—</td>
</tr>
</tbody>
</table>

Source: A305 Clinical Study Report, Table 10, verified by FDA statistical reviewer.
* The corresponding p-value was <0.001.

Abbreviations: CI = unadjusted confidence interval, LS = least-squares, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, SE = standard error.

To assess the robustness of the primary analysis, the Applicant prespecified a sensitivity analysis using a delta-adjusted Pattern Mixture Model as for study A303. This model incorporated the clinical assumption that ALKS 3831-treated subjects who discontinued at a given time point would have, on average, their unobserved PANSS worsened by some amount δ compared with the observed PANSS of subjects on the same treatment arm who continued to the next time point, and that subjects who discontinued from the olanzapine arm would have the same PANSS trajectory as the olanzapine-treated subjects who stayed on the study.

The sensitivity analysis results are very robust in support of the primary analysis, even when the ALKS 3831-treated subjects who dropped out are assumed to have PANSS outcomes worsened by up to 3.2 points more than ALKS 3831-treated subjects whose PANSS scores were collected.

3.1.4. Studies ALK3831-A304 and ALK3831-A306

ALK3831-A304 and ALK3831-A306 were the open-label (OL) extension studies of Study A303 and Study A305, respectively. Enrolled subjects were assessed over 52 weeks to evaluate ALKS 3831’s long-term safety and tolerability. The efficacy endpoint of PANSS total score change from baseline appeared stable over the course of the studies. There was no comparator arm in either long-term study.

The effect on weight from switching from olanzapine to ALKS 3831 was assessed from the transition from the two phase 3 pivotal studies (A303 and A305) to their respective OL safety extension studies. Group 1 comprised the acutely ill subjects from Study A305; Group 2 comprised the stable subjects from Study A303 (see Figure 15). Of note, the populations are not considered representative of the controlled data, as (1) only data from subjects who chose to continue in the OL studies are available and (2) the switch analysis only included subjects exposed to ALKS 3831 (i.e., subjects taking olanzapine or placebo were only included if they were exposed to ALKS 3831 during the OL study — subjects taking ALKS 3831 during Study A303 or Study A305 were included in the switch analysis if they had postbaseline visits whether or not they received ALKS 3831 during the OL studies). Therefore, the numbers of subjects in the OLZ/ALKS 3831, ALKS 3831/ALKS 3831, and PBO/ALKS 3831 treatment sequences were not necessarily representative of their original randomization.
In Group 1 (Study A306; acutely ill), the weight trajectories of subjects who switched from placebo or olanzapine to ALKS 3831 showed initial increases in weight, which, according to the Applicant, stabilized by approximately 4 weeks to 6 weeks after the switch.

In Group 2 (Study A304; stable), mean changes in weight during Study A303 in subjects who switched from olanzapine to ALKS 3831 in the OL extension were 4.28 kg (5.60%; reflecting olanzapine weight gain) and 5.02 kg (6.43%) from the Study A303 baseline to Week 12 of the OL extension (i.e., 36 weeks after A303 baseline). Thereafter, the mean weight gain “stabilized” at subsequent visits (e.g., 4.30 kg (5.39%) from the A303 baseline at OL 28 weeks (52 weeks after A303 baseline) and 3.63 kg (4.49%) from the A303 baseline at OL 52 weeks (76 weeks after the A303 baseline)). However, the subject population is not representative of the original randomized groups, for the reasons stated above.
Figure 15. Mean Percent Change from Baseline in Body Weight by Visit and Treatment Sequence Through Week 12 of the Extension Study

Source: Integrated Summary of Efficacy, Figure 38

Note: Baseline is defined as the last nonmissing value on or before the first dose of study drug in Study A305 for the Group 1 figure and in Study A303 for the Group 2 figure. The numbers in the bottom rows indicate the numbers of subjects with assessment at each week.

Group 1: Studies A305 and A306; acutely ill. Group 2: Studies A303 and A304; stable.

Abbreviations: ISE = Integrated Summary of Efficacy, OLZ = olanzapine, PBO = placebo, SE = standard error.
As discussed in Section 2.3, historical olanzapine data suggest that the trajectory of weight gain may continue to increase over time. The Applicant presented a comparison of long-term ALKS 3831 data with historical olanzapine data, potentially suggesting less weight gain over time with ALKS 3831, as compared with long-term use of olanzapine, see Figure 16.

Figure 16. Side-by-Side View of Historical Weight Results in Long-Term OLZ Studies and Long-Term Weight Results for ALKS 3831

However, this comparison is limited by missing data, the fact that Study A304 was ongoing at the time of data lock, data pooling (resulting in different baselines and populations as described below), as well as the general limitations of cross-study comparisons (Laubach et al. 2014). According to the referenced publication that provided historical data for Figure 16, while 12,425 subjects were evaluated in the meta-analysis of long-term olanzapine data, the N at Month 1 was 10,795 and the N at Month 18 (approximately 76 weeks) was 388 (Millen et al. 2011). The ALKS 3831 data from the NDA integrated a number of different data streams, starting from the first exposure of ALKS 3831 through the entire treatment period across multiple studies.\(^4\) Finally, the Applicant did not present a comparison of subject characteristics or other findings that could support or confound this interpretation of weight gain with ALKS 3831 versus olanzapine over the long-term.

\(^4\)The study in which initiation of ALKS 3831 occurred varied depending on whether the subject was randomized to ALKS 3831, OLZ, or placebo in the controlled study. Baseline was defined as the last non-missing value on or before the first dose of ALKS 3831.
In Study A304 and Study A306, metabolic laboratory parameters were monitored as part of the safety assessment only. Given an absent comparator arm, this data is compared to historical data from the Zyprexa label and four long-term studies. However, such a comparison is significantly limited, as discussed above. As measured by fasting glucose change from baseline and proportion of subjects experiencing potentially clinically significant glucose and HbA1c levels (with the exception of subjects with a transition from normal to borderline-high glucose), subjects receiving open-label ALKS 3831 experienced similar or favorable glycemic changes when compared to historical data. Similarly, as measured by fasting lipid profile changes from baseline and proportion of subjects experiencing potentially clinically significant levels (with the exception of subjects with abnormal LDL), subjects experienced similar or favorable lipid profile changes when compared to historical data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study A304</th>
<th>Study A306</th>
<th>Zyprexa Label</th>
<th>CATIE Study (Lieberman et al. 2005)</th>
<th>EUFEST Study (Kahn et al. 2008)</th>
<th>CAFE Study (McEvoy et al. 2007)</th>
<th>(Kinon et al. 2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration</td>
<td>52 weeks</td>
<td>52 weeks</td>
<td>&gt;48 weeks</td>
<td>18 months</td>
<td>52 weeks</td>
<td>52 weeks</td>
<td>1 to 3 years</td>
</tr>
<tr>
<td>N (completed/enrolled)</td>
<td>167/265</td>
<td>183/277</td>
<td>Up to 2021</td>
<td>120/330</td>
<td>75/104</td>
<td>42/133</td>
<td>147/573</td>
</tr>
<tr>
<td>Body weight (kg), mean change (SD)</td>
<td>-0.03 (6.2)</td>
<td>1.9 (6.7)</td>
<td>5.6</td>
<td>4.3</td>
<td>13.9 (1.7)</td>
<td>11.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Glucose (mg/dL), mean change (SD)</td>
<td>1.3 (16.0)</td>
<td>5.9 (17.2)</td>
<td>4.2</td>
<td>15 (2.8)</td>
<td>9</td>
<td>8.6 (1.6)</td>
<td>—</td>
</tr>
<tr>
<td>HbA1c (%) , mean change (SD)</td>
<td>0.03 (0.3)</td>
<td>-0.06 (0.4)</td>
<td>0.41 (0.09)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL), mean (SD)</td>
<td>-2.4 (26.5)</td>
<td>-1.8 (33.3)</td>
<td>5.6</td>
<td>9.7 (2.1)</td>
<td>30.9</td>
<td>15.7 (4.3)</td>
<td>—</td>
</tr>
<tr>
<td>HDL (mg/dL), mean change (SD)</td>
<td>1.3 (11.5)</td>
<td>1.1 (12.5)</td>
<td>-0.2</td>
<td>—</td>
<td>-3.9 (0)</td>
<td>-6.5 (0.9)</td>
<td>—</td>
</tr>
<tr>
<td>LDL (mg/dL), mean change (SD)</td>
<td>-1.5 (25.5)</td>
<td>0.9 (30.6)</td>
<td>2.5</td>
<td>—</td>
<td>27.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TG (mg/dL), mean change (SD)</td>
<td>-10.7 (85.6)</td>
<td>8.1 (74.0)</td>
<td>18.7</td>
<td>42.9 (8.4)</td>
<td>26.6</td>
<td>66.4</td>
<td>(12.9)</td>
</tr>
<tr>
<td>Parameters</td>
<td>Study A304</td>
<td>Study A306</td>
<td>Zyprexa Label</td>
<td>CATIE Study (Lieberman et al. 2005)</td>
<td>EUFEST Study (Kahn et al. 2008)*</td>
<td>CAFE Study (McEvoy et al. 2007)</td>
<td>CAFE Study (Kinon et al. 2001)*</td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------------------------</td>
<td>----------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Weight gain &gt;7% body weight</td>
<td>16.1</td>
<td>27.6</td>
<td>64</td>
<td>30</td>
<td>86</td>
<td>80</td>
<td>52</td>
</tr>
<tr>
<td>Total cholesterol ≥240 mg/dL*</td>
<td>10.1</td>
<td>14.8</td>
<td>14.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>15.7</td>
</tr>
<tr>
<td>LDL ≥160 mg/dL*</td>
<td>13.5</td>
<td>16.8</td>
<td>7.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HDL &lt;40 mg/dL*</td>
<td>15.3</td>
<td>26.6</td>
<td>—</td>
<td>25</td>
<td>48.9-50*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TG ≥200 mg/dL*</td>
<td>16.7</td>
<td>24.0</td>
<td>32.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glucose normal (&lt;100 mg/dL) to high (≥126 mg/dL)</td>
<td>9.7</td>
<td>7.6</td>
<td>12.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glucose normal (&lt;100 mg/dL) to borderline/high (≥100 mg/dL)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>57</td>
<td>—</td>
<td>25.5</td>
<td>—</td>
</tr>
<tr>
<td>Glucose borderline (≥100 mg/dL to &lt;126 mg/dL) to high (≥126 mg/dL)</td>
<td>16.2</td>
<td>18.8</td>
<td>26.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Source: Reviewer generated.

* Changes from normal or borderline to high/low.

* Note that this was an OL study in subjects with early illness.

* Note that this was a retrospective study with some subjects receiving OL treatment.

* Female subjects in this study had a cutoff of <50 mg/dL.

Abbreviations: HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, N = number of subjects, SD = standard deviation, TG = triglycerides

As previously mentioned, significant factors impacting interpretability of these metabolic data from study ALK3831-A304 and study ALK3831-A306 include: (1) only data from subjects who chose to continue in the OL studies are available, (2) absence of comparator arm, (3) missing data, and (4) the general limitations of cross-study comparisons.

In summary, the switch analysis and long-term analysis of weight and metabolic data comparing to historical olanzapine data have numerous limitations and should be interpreted with caution.

### 3.2. SAFETY OF ALKS 3831

#### 3.2.1. Adverse Events and Investigations

ALKS 3831 shares a similar safety profile to other drugs in the atypical antipsychotic class—these were evaluated as AEs of special interest. However, there were no new safety signals.

Three deaths occurred in ALKS 3831 development programs, but all were unlikely related to treatment. In a phase 2 study of subjects with schizophrenia and co-occurring alcohol use disorder, one subject randomized to ALKS 3831 treatment died secondary to complications of chronic obstructive pulmonary disease exacerbation; this subject also experienced an AE of
weight gain during treatment. A second subject in this study, randomized to olanzapine treatment (although he also received 14 days of open-label ALKS 3831 treatment prior to randomization), died from alcohol poisoning; he did not report any AEs during treatment. These two deaths were likely attributable to premorbid and comorbid conditions, respectively. In Study A305, one subject randomized to olanzapine treatment died secondary to a heroin overdose. This subject had a history of methamphetamine abuse and also experienced AEs of dizziness and weight gain during treatment. This death was unlikely related to treatment but highlights the potential for opioid misuse in this patient population.

Commonly reported AEs occurring in \( \geq 5\% \) of subjects receiving ALKS 3831 included: weight increased, somnolence, dry mouth, headache, anxiety, increased appetite, fatigue, infection, waist circumference increased, upper respiratory infection, extra dose administered, and blood CK increased. Rates for these AEs were generally similar for both ALKS 3831 and olanzapine groups, except in Study A303, somnolence, dry mouth and fatigue occurred more frequently with ALKS 3831 treatment. Rates of serious adverse events and AEs leading to study discontinuation were similar between the two treatment groups.

Investigations revealed some laboratory result and vital sign abnormalities—the majority likely represent class effects, and most differences between ALKS 3831 and olanzapine were small. Refer to Section 3 for discussions of weight gain and metabolic laboratory findings. Other class effects were observed: changes in liver function, prolactin levels, and neutrophil and leukocyte values, orthostatic hypotension, QTc shifts, and extrapyramidal symptoms. In Study A305, clinically significant changes in standing heart rate and postural tachycardia occurred with slightly greater frequency with ALKS 3831 compared to olanzapine and, in Study A303, changes in supine heart rate occurred with slightly greater frequency with ALKS 3831 compared to olanzapine. However, differential occurrence was small (4% with ALKS 3831, \( \leq 1\% \) with olanzapine), and there was no consistent trend to indicate a clinically significant signal. In Study A303, a comparison of mean shift from baseline to final treatment visit supine SBP favored ALKS 3831 over olanzapine—but this may be a spurious finding as there were no meaningful differences in standing SBP measurements, all-treatment-visit measurements, rates of abnormally elevated SBP, and reported AEs.

3.2.2. Safety Concerns Regarding Precipitated Opioid Withdrawal, Inadequate Analgesia, and Opioid Overdose

There are potential safety risks that will need to be considered with the inclusion of samidorphan in the proposed fixed-dose combination product—namely, whether samidorphan’s opioid antagonist action may precipitate withdrawal in patients who are physically dependent on opioids, and whether samidorphan use could lead to ineffective analgesia when medically necessary, or inadvertent blocking of a high in those with an opioid use disorder. These latter situations could also result in overdose as a patient attempts to overcome samidorphan’s opioid antagonist effects.

Opioid use was an exclusion criterion for ALKS 3831 clinical studies by way of history, drug screens, and ascertainment of concomitant medications. Therefore, assessment for opioid withdrawal, inadequate analgesia, and opioid overdose was limited; however, the potential for these adverse safety outcomes in postmarket settings of use warrants consideration.
**Clinical Trial Data**

In a phase 1 samidorphan-only trial enrolling nondependent but opioid-experienced subjects, there was one incident of precipitated opioid withdrawal. The subject was a healthy participant who did not disclose opioid dependence history at enrollment and had a negative urine drug screen at screening. He experienced symptoms of withdrawal 2 minutes after administration of samidorphan 10 mg and subsequently received treatment during hospital admission; the subject was deemed stable at 24 hours. At study follow-up 2 days later, his drug screen was positive for opioids, THC, and benzodiazepines; at follow-up 9 days later, his drug screen was positive for cocaine. However, there was no AE pattern in study A303 or study A305 that may have represented opioid withdrawal symptoms (consistent with the exclusion of people with opioid use)—nor was there any report of inadequate opioid analgesia or opioid overdose.

To monitor for samidorphan-related withdrawal, the Applicant recorded AEs during a 2-week follow-up period after study drug treatment ended in subjects who did not continue to the open-label extension studies. No signals emerged based on these AEs: rates of nonspecific symptoms (nausea, depression, insomnia, tachycardia, tremor, vomiting, agitation, and headache) were unremarkable (all less than 1%).

Upon ascertainment of concomitant medications, 18 subjects reported opioid exposure while receiving ALKS 3831. Of these, two were exposed to opioids for more than a short-term duration (13 days and 37 days). For one subject, ALKS 3831 treatment was temporarily interrupted, but then continued and overlapped with concomitant oral oxycodone for 10 days. The other subject completed ALKS 3831 treatment 1 day after opioid treatment was initiated. None of the 18 subjects reported inadequate analgesia; however, this was not specifically asked during the study and it is unknown if the subjects took a higher dose of opioids while on ALKS 3831 than they would have otherwise.

Three subjects had documented opioid abuse AEs: Two subjects in extension study A304 were found to have urine drug screens positive for opiates. One of these subjects had a drug screen positive for opiates and cocaine on day 239; he did not have any other reported AEs during study A303 and study A304. The other subject had a drug screen positive for opiates and methamphetamine on day 222 when he was hospitalized for a pulmonary embolism; he also experienced the AE of decreased appetite. Another subject with documented history of drug abuse (negative baseline drug screen) and receiving ALKS 3831 in study A303 reported heroin use on day 97, but later described this as a misrepresentation of his drug use (he had actually used cannabis) to gain hospital admission. During inpatient treatment, he received nicotine, buprenorphine, quetiapine, clonidine, and thiamine. There was no drug screen result available for confirmation. The subject did not have reported AEs 3 days before and after this event; however, other reported AEs during treatment outside this window include blood pressure increased, dry mouth, extra dose administered, increased appetite, lethargy, toothache, upper respiratory tract infection, waist circumference increased, and weight increased.

Additionally, in Study A308, a subject was hospitalized for an accidental oxycodone overdose leading to discontinuation of study drug: he reported ingesting four tablets of acetaminophen, but presentation and drug testing confirmed presence of oxycodone and absence of acetaminophen. Further narrative was not provided.
Additional Considerations Based on Epidemiologic Literature (See Appended Division of Epidemiology Review for Further Detail and References):

Overall, there are no new safety signals with ALKS 3831. Epidemiological data provide some context for the overall benefit-risk assessment of samidorphan.

Chronic use of opioids and opioid dependence were proposed by the Applicant as contraindications for ALKS 3831. However, it is important to consider scenarios where a prescriber may be unaware of a patient’s opioid use, including when the patient is using opioids nonmedically (e.g., taking opioids at higher doses or for longer than directed, obtaining opioids from a source other than their own prescription) or when a patient has an undisclosed opioid use disorder. One safety concern is the potential for inadvertently precipitating opioid withdrawal in patients who are opioid dependent, either through medical or nonmedical chronic opioid exposure. Epidemiologic studies show an association between bipolar disorder and chronic pain conditions (Birgenheir et al. 2013). In one U.S. study, the percentage of patients with bipolar disorder who reported chronic opioid use was three times higher than patients without bipolar disorder (Owen-Smith et al. 2020).

Epidemiologic data also suggest a higher prevalence of nonmedical opioid use and opioid use disorder in people with bipolar disorder relative to the general population. Based on national survey data, those who report nonmedical opioid use at baseline have approximately 1.7 times the risk of new bipolar diagnosis, compared to those without nonmedical opioid use; and individuals with bipolar disorder at baseline have approximately 1.7 times the risk of subsequent nonmedical opioid use compared to those without bipolar disorder at baseline (Martins et al. 2012). Those with opioid use disorder at baseline also have approximately 1.5 to 1.9 times the risk of new bipolar diagnosis, although those with bipolar disorder at baseline had a similar risk of subsequent opioid use disorder, compared to those without bipolar disorder at baseline (Martins et al. 2012; Saha et al. 2016).

Additionally, a study of patients with bipolar disorder receiving care at a Veterans clinic reported a prevalence of opioid use disorder at 2.7% (Bauer et al. 2005). Considering the estimated prevalence of nonmedical opioid use (3.6%) or opioid use disorder (0.7%) in the general U.S. population (Substance Abuse and Mental Health Services Administration 2019), we estimate that the percentage of individuals with bipolar disorder who use opioids nonmedically in a given year may be greater than 5%, and the percentage of individuals with bipolar disorder who have an opioid use disorder may be in the range of 1 to 3%, depending on other characteristics of the patient population.

All of these estimates are approximate, as there are no current, direct data on the prevalence of opioid use disorder among those with bipolar disorder, likely due to the challenging nature of this population to study and lack of reliable measures (i.e., claims-based algorithms) of opioid use disorder that can be linked to these diagnoses. In addition, the prevalence of opioid nonmedical use and opioid use disorder likely varies considerably across different patient populations.

Data are sparse on nonmedical opioid use and opioid use disorder in patients with schizophrenia. Older survey data suggest that the percentage of individuals with schizophrenia who use opioids
nonmedically may be many times higher than in patients without mental illness (Regier et al. 1990; Martins and Gorelick 2011); however, more recent, smaller studies suggest that individuals with schizophrenia and substance use disorders may prefer other drugs to opioids.

A 2017 review of postmarket cases in the FDA Adverse Event Reporting System (FAERS) and the National Poison Data System (NPDS) identified adverse events potentially related to opioid withdrawal reportedly occurring when an approved, naltrexone-containing product (bupropion-naltrexone) was used with an opioid. At the time of the review, just over 2 years of postmarketing data were available, yielding 69 cases in FAERS and 22 cases in NPDS. Though the majority of the cases were mild, there were a few cases of more severe events such as seizures that required hospitalization. These cases provide some evidence that in a population not currently being treated for opioid use disorder, adverse events potentially related to opioid withdrawal can occur when an opioid antagonist-containing product is used in the setting of opioid use.

Another possible scenario is a patient taking ALKS 3831 who develops a severe pain condition requiring opioid analgesics. If the analgesic effect is reduced due to samidorphan’s opioid receptor antagonism, the patient could experience inadequate pain control and may increase their dose to overcome the antagonist blockade. This could put the patient at elevated risk for opioid overdose if the samidorphan effect wanes or fluctuates (i.e., with discontinuation or missed doses), exposing the patient to a high level of unopposed opioid agonist. A recent FDA analysis of retail pharmacy dispensing data found that roughly one in five patients dispensed olanzapine received a concomitant prescription for an opioid analgesic within 1 year, suggesting that a substantial proportion of individuals prescribed ALKS 3831 may, at some point, require opioid pain medication and be at risk for inadequate analgesia and, perhaps, opioid overdose.

In addition, the 2017 review of bupropion-naltrexone indicated that 11% of patients on bupropion-naltrexone had a concurrent claim for opioid products, despite their contraindication in labeling, suggesting that despite ALKS 3831’s proposed labeling, concurrent use of opioids would likely occur in the patient population. Due to limitations in the data sources, the FDA review was unable to determine the reason for co-prescribing despite the contraindication in bupropion-naltrexone labeling. It is also notable that the concurrency analysis used national projections generated from outpatient retail dispensing claims, and outcome data were not available. Thus, the FDA review could not determine the actual risk of opioid overdose in these patients. Individuals prescribed ALKS 3831 who use opioids nonmedically could theoretically also be at risk for overdose if they attempt to overcome samidorphan’s opioid blockade.

A final scenario to consider are patients who stop chronic opioids, initiate ALKS 3831, and then discontinue ALKS 3831 and resume opioid use. If these patients resume the opioid dose they had initially been taking, they may be at elevated risk of opioid overdose due to a loss of opioid tolerance. Epidemiologic studies suggest that patients being treated for opioid use disorder with naltrexone have a period of increased opioid overdose risk immediately following naltrexone discontinuation (or when the antagonist effect wanes, in the case of depot naltrexone) (Morgan et

However, it should be noted that these studies have been conducted in populations being treated for opioid use disorder, who are likely to be at greater risk of opioid overdose than the ALKS 3831 indicated patient population.

In summary, there are no new antipsychotic-related safety signals identified in the ALKS 3831 clinical trial program. However, the potential safety concerns related to the opioid antagonism of the samidorphan component in various real-world settings of opioid use warrant consideration. These include the potential for precipitated withdrawal, inadequate analgesia, and opioid overdose. The epidemiologic data suggest that a subset of the indicated patient population could theoretically be at risk for one or more of these adverse events in postmarket settings, considering the relatively high prevalence of chronic pain and chronic opioid use in patients with bipolar disorder, the substantial use of concomitant opioids in patients receiving olanzapine, and data suggesting an elevated risk of nonmedical opioid use and opioid use disorder in individuals with bipolar disorder and possibly schizophrenia.
4. REFERENCES


Birgenheir, DG, MA Ilgen, AS Bohnert, KM Abraham, NW Bowersox, K Austin, and AM Kilbourne, 2013, Pain conditions among veterans with schizophrenia or bipolar disorder, Gen Hosp Psychiatry, 35(5):480-484.


Draft guidance for industry Developing Products for Weight Management Revision 1 (February 2007).


Lipkovich, I, JG Jacobson, TA Hardy, and VP Hoffmann, 2008, Early evaluation of patient risk for substantial weight gain during olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder, BMC Psychiatry, 8:78.


Olfson, M, T Gerhard, C Huang, S Crystal, and TS Stroup, 2015, Premature Mortality Among Adults With Schizophrenia in the United States, JAMA Psychiatry, 72(12):1172-1181.


2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH series H-54) Key Substance Use and Mental Health Indicators in the United States (Substance Abuse and Mental Health Services Administration 2019).
### 5.1. STUDY ASSESSMENT SCHEDULES

#### Table 16. Assessment Schedule for A303

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening Day -30 to -1</th>
<th>24-Week Double-Blind Treatment</th>
<th>Safety Follow-up</th>
<th>Monthly Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2^t 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17/ET 18 19 20 to 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Week (Visit Window of ±2 Days for Visits 3-24)</td>
<td>1 2 3 4 5 6 8 10 12 14 16 18 20 22 24</td>
<td>26 28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Qualification/ Diagnostic Assessments

- Informed Consent
- Eligibility Criteria Review
- Demographics and Medical/ Psychiatric History Review
- MINI
- Height

#### Qualification/ Safety Assessments

- Serology Testing^6
- Pregnancy Test^6
- Drug Screen^2
- Physical Exam^2
- 12-lead ECG
- AIMS
- SAS
- BARS
- Biochemistry, Urinalysis, and Hematology Samples^3
- Vital Signs^3
- Body Weight and Waist Circumference^2
- AE Monitoring
- Concomitant Medication Review^2
- C-SSRS^8

#### Psychiatric/ Efficacy/ Lifestyle/ Quality of Life Assessments

- PANSS^4
- CGI-S
- CGI-I
- Cigarette Use Questionnaire
- IWQOL-Lite
- EQ-5D-3L

#### Other/ General Procedures

- Randomization
- Genotype Sample
- PK Labs^6
- Study Drug Dispensation
- Study Drug Return and Adherence Review
- Emergency Treatment Card^8

Source: A303 Clinical Study Report, Table 3.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CGI-I = Clinical Global Impression-Improvement, CGI-S = Clinical Global Impression-Severity, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, IWQOL = Impact Weight on Quality of Life, MINI = Mini International Neuropsychiatric Interview, PANSS = Positive and Negative Syndrome Scale, PK = pharmacokinetic, SAS = Simpson-Angus Scale.
Table 17. Assessment Schedule for A305

<table>
<thead>
<tr>
<th>Period</th>
<th>Screening</th>
<th>Double-Blind Treatment Period</th>
<th>Follow-Up&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Study Day</td>
<td>-10 to -1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/ Psychiatric History</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini International Neuropsychiatric Interview (MIND)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Criteria Review</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Genotype Sample</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight and waist circumference (conducted 3 times each visit)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical Examination&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Testing</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serology Testing&lt;sup&gt;7&lt;/sup&gt;</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Laboratory Samples&lt;sup&gt;3&lt;/sup&gt; (refer to Table 2 of the protocol)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PK Sample&lt;sup&gt;8&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital Signs&lt;sup&gt;10&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12-Lead Electrocardiogram</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Monitoring</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medication Review</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Abnormal Movement Scales&lt;sup&gt;12&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale (PANSS)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Modified Overt Aggression Scale&lt;sup&gt;14&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Global Impression – Severity (CGI-S)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>X&lt;sup&gt;16&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Global Impression – Improvement (CGI-I)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Informed Consent for ALK3831-A306</td>
<td>X&lt;sup&gt;17&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>Emergency treatment card&lt;sup&gt;18&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Admission to Inpatient Unit&lt;sup&gt;19&lt;/sup&gt;</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from Inpatient Unit&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study Drug Dispensation&lt;sup&gt;21&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study Drug Return and Adherence Review</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Source: A305 Clinical Study Report, Table 3.
Abbreviation: PK = pharmacokinetic
5.2. Weight Gain Trajectories by Dropout Reason (Study A303)

Figure 17: Weight Gain Trajectories of Individual Dropouts with Top Three Discontinuation Reasons (Study A303)

Performed on the primary efficacy analysis set.
Note: Each line represents an individual subject’s observed percent weight gain trajectory. Different colors represent different discontinuation reasons: red: adverse events; purple: withdrawal by subject; black: loss to follow-up. Dotted gray lines represent completers as a reference.
Source: FDA statistical reviewer.
Epidemiology and Drug Utilization Review: Assessment of the Potential Risks Associated with Using Olanzapine/Samidorphan with Opioids

Date: 9/11/2020

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Grace Chai, PharmD, Associate Director for Special Initiatives Office of Surveillance and Epidemiology

Subject: Assessment of the Potential Risks Associated with Using Olanzapine/Samidorphan with Opioids

Drug Name: Lybalvi

Application Type/Number: NDA 213378
Applicant/sponsor: Alkermes, Inc.

OSE RCM #: 2019-2354

**This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.**
LIST OF ABBREVIATIONS:

FAERS: FDA Adverse Event Reporting System
FDA: Food and Drug Administration
NESARC: National Epidemiological Survey on Alcoholism and Related Conditions
NPA: National Prescription Audit™
NSDUH: National Survey on Drug Use and Health
NP: Nurse Practitioner
NPDS: National Poison Data System
NSP: National Sales Perspectives™
PA: Physician Assistant
SAMHSA: Substance Abuse and Mental Health Services Administration
SH: Symphony Health™
US: United States
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EXECUTIVE SUMMARY

Olanzapine/samidorphan (NDA #213378) is a combination of olanzapine, an atypical antipsychotic, and samidorphan, an orally bioavailable µ-opioid antagonist. This drug is indicated for treatment of (1) schizophrenia in adults and (2) bipolar I disorder in adults, including acute treatment of manic episodes as monotherapy and as maintenance monotherapy treatment, and adjunct to valproate or lithium in the treatment of manic or mixed episodes. In this combination product, samidorphan is intended to mitigate olanzapine-induced weight gain.

The purpose of this review is to provide epidemiologic data to inform discussion of the potential risks associated with use of olanzapine/samidorphan in the setting of acute or chronic opioid use (either medical or nonmedical). This review addresses the following topics: 1) the associations between bipolar disorder or schizophrenia, chronic pain, and opioid nonmedical use, 2) utilization patterns of olanzapine and opioid-containing products, including concomitant use of these medications, and 3) epidemiology of opioid overdose or withdrawal associated with use of oral naltrexone, the only orally bioavailable µ-opioid antagonist marketed in the United States.

Although chronic use of opioids and opioid dependence are proposed contraindications for olanzapine/samidorphan, it is important to consider the opioid antagonist effect of samidorphan and the safety implications of this for patients with acute or chronic pain conditions requiring opioids or who use opioids nonmedically. One safety concern is the potential for inadvertently precipitating opioid withdrawal in patients who are opioid dependent, either through medical or nonmedical chronic opioid exposure.

Epidemiologic data suggest that chronic opioid use is relatively common among patients with bipolar disorder. In one large sample of adults with bipolar disorder, 10.4% were categorized as receiving a chronic opioid prescription, compared with 3.0% for patients without bipolar disorder. Results were mixed for schizophrenia with regard to whether these patients had a higher prevalence of chronic pain and opioid use, compared to those without schizophrenia.

Epidemiologic data also indicate that bipolar disorder is associated with both nonmedical opioid use and opioid use disorder. A large nationally representative survey on alcohol use disorder, drug use disorders, and comorbidities found that individuals with opioid nonmedical use at baseline had approximately 1.7 times the risk of new bipolar disorder diagnosis as compared to people without baseline opioid nonmedical use; and individuals with bipolar disorder at baseline had approximately 1.7 times the risk of subsequent nonmedical opioid use compared to those without bipolar disorder at baseline.

Individuals with baseline opioid use disorder or dependence had approximately 1.5-1.9 times the risk of a new diagnosis of bipolar disorder, although those with bipolar disorder at baseline had a similar risk of subsequent opioid use disorder, compared to those without bipolar disorder at baseline. Additionally, a study of individuals receiving care at
a Veterans Affairs clinic reported the prevalence of opioid use disorder among patients with bipolar disorder at 2.7%. Given the estimated prevalence of opioid nonmedical use (3.6%) or opioid use disorder (0.7%) in the general population, based on the most recent data from the National Survey on Drug Use and Health (NSDUH), and the associations found in these studies, we estimate that the percentage of individuals with bipolar disorder who use opioids nonmedically may be greater than 5%, and the percentage of the population with bipolar disorder who have opioid use disorder may be in the range of 1%-3%. All of these estimates are approximate, as there is not current, direct data on the prevalence of opioid use disorder among those with bipolar disorder, likely due to the challenging nature of this population to study and lack of reliable measures (i.e., claims-based algorithms) of opioid use disorder that can be linked to these diagnoses. In addition, prevalence of opioid nonmedical use and opioid use disorder likely varies considerably across different patient populations.

Data are sparse on nonmedical opioid use and opioid use disorder in patients with schizophrenia. Some studies of individuals seeking treatment for substance use disorders suggest that individuals who report nonmedical substance use with co-occurring schizophrenia are less likely to prefer opioids as compared to individuals who report nonmedical substance use with no co-occurring mental health disorder. However, older national survey data suggest that the percentage of individuals with schizophrenia who use opioid nonmedically may be many times higher than in patients without mental illness.

A 2017 review of postmarket cases in FDA Adverse Event Reporting System (FAERS) and the National Poison Data System (NPDS) identified adverse events potentially related to opioid withdrawal reportedly occurring when an approved, naltrexone-containing product (bupropion/naltrexone) was used with an opioid. At the time of the review, just over two years of postmarketing data were available, yielding 69 cases in FAERS and 22 cases in NPDS. Though the majority of the cases were mild, there were a few cases of more severe events such as seizures that required hospitalization. These cases provide some evidence that in a population not currently being treated for opioid use disorder, adverse events potentially related to opioid withdrawal can occur when an opioid antagonist-containing product is used in the setting of opioid use.

Another safety concern involves a scenario where a patient taking olanzapine/samidorphan develops a severe pain condition requiring opioid analgesics. If the analgesic effect is reduced due to samidorphan’s opioid receptor antagonism, the patient could experience inadequately controlled pain and might also increase their opioid dose to overcome the antagonist blockade. This could put the patient at higher risk for opioid overdose as the samidorphan effect wanes or fluctuates, exposing the patient to high levels of unopposed opioid agonist. Based on FDA’s analysis of drug utilization data, among patients with olanzapine prescription claims in 2019, approximately 21%
(339,000 patients) had concurrent (overlapping days’ supply of at least 1 day from both the base group and the concurrent group) opioid prescription claims, either analgesics or cough/cold products. A 2017 FDA safety review of bupropion/naltrexone indicated that 11% of patients on bupropion/naltrexone had a concurrent claim for opioid products, despite their contraindication in labeling, suggesting that despite the proposed labeling for olanzapine/samidorphan, concurrent use of opioids would likely occur. The concurrency analysis used national projections generated from outpatient retail dispensing claims; as patient outcome data were not available, the FDA review could not assess risk of opioid overdose in these patients.

A final safety scenario to consider is a patient who tapers off chronic opioids to initiate olanzapine/samidorphan, and later discontinues olanzapine/samidorphan and resumes opioid use. If the patient resumes their previous opioid dose, they may be at elevated risk of opioid overdose due to loss of opioid tolerance. Epidemiologic literature suggests that patients being treated for opioid use disorder with naltrexone (an opioid receptor antagonist) have a period of increased opioid overdose risk immediately following naltrexone discontinuation. It should be noted that these studies only include patients being treated for opioid use disorder and are therefore likely to be at greater risk for opioid overdose than the patient population for which olanzapine/samidorphan is indicated.

The potential safety concerns related to samidorphan’s opioid antagonist effect in various real-world settings of opioid use warrant careful consideration. These concerns include the potential for precipitated opioid withdrawal, inadequate analgesia, and opioid overdose. The epidemiologic data suggest that a substantial subset of the indicated patient population could be at risk for one or more of these adverse events.

1 INTRODUCTION
Olanzapine/samidorphan (NDA #213378) is a combination of olanzapine, an atypical antipsychotic, and samidorphan, an orally bioavailable µ-opioid antagonist. This drug is indicated for treatment of (1) schizophrenia in adults and (2) bipolar I disorder in adults, including acute treatment of manic episodes as monotherapy and as maintenance monotherapy treatment, and adjunct to valproate or lithium in the treatment of manic or mixed episodes. Olanzapine is currently marketed as an atypical antipsychotic, but this is the first olanzapine antipsychotic in combination with samidorphan. Samidorphan is a new molecular entity, and thus is not currently marketed in the United States (U.S.) In this combination product, samidorphan is intended to mitigate olanzapine-induced weight gain.

In assessing the benefits and risks of this combination product, it is important to consider the full µ-opioid antagonist effect of samidorphan and the safety implications of this for patients with acute or chronic pain conditions or who use opioids nonmedically.
Although chronic use of opioids and opioid dependence are contraindications for olanzapine/samidorphan, it is important to consider the potential impact for patients in the indicated population who might require an opioid analgesic for unexpected acute, severe pain or for whom a prescriber may be unaware of a patient’s opioid use, particularly if opioids are being used nonmedically (e.g., obtaining them from a source other than their own prescription) or if the patient has an undisclosed opioid use disorder. One concern is the potential for inadvertently precipitating opioid withdrawal in patients who are opioid dependent, either through medical or nonmedical chronic opioid exposure. Another concern is the potential for inadequate control of unexpected, acute, severe pain in patients receiving olanzapine/samidorphan. Finally, patients taking olanzapine/samidorphan may have an increased risk for opioid overdose if high doses of opioids are used to overcome samidorphan’s antagonist effects (either to manage pain or in the setting of nonmedical use or an opioid use disorder), or if a previously high dose of opioid is resumed following olanzapine/samidorphan discontinuation.

In a phase 1 study (ALK33-004) with samidorphan, one patient enrolled in the trial did not disclose their long-term opioid dependence, and the presence of samidorphan in their system precipitated opioid withdrawal. This patient was withdrawn from the clinical trial. Although opioid use is contraindicated with olanzapine/samidorphan, this example demonstrates the need to consider adverse events that may occur for patients who use opioids, either medically or nonmedically, while taking olanzapine/samidorphan.

The purpose of this review is to provide epidemiologic data to inform discussion of the potential risks associated with use of olanzapine/samidorphan in the setting of acute or chronic opioid use (either medical or nonmedical). This review addresses the following topics: 1) associations between bipolar disorder or schizophrenia, chronic pain, and opioid nonmedical use, 2) utilization patterns of olanzapine and opioid-containing products, including concomitant use of these medications, and 3) epidemiology of opioid overdose or opioid withdrawal associated with use of oral naltrexone, the only orally bioavailable μ-opioid antagonist marketed in the U.S.

2 REVIEW METHODS AND MATERIALS

2.1 TERMINOLOGY

FDA has previously established standard regulatory definitions of misuse and abuse,1 as described below. This review combines these definitions into a composite term, nonmedical use. FDA acknowledges concerns about stigma associated with some terminology related to substance use disorders, including the term abuse among others, as well as the importance of reducing use of stigmatizing language to reduce barriers to care and address the nation’s public health crisis of addiction and overdose.
**Misuse:** intentional use, for therapeutic purposes, of a drug in a way other than prescribed or by an individual for whom it was not prescribed.

**Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects.

### 2.2 DRUG UTILIZATION

We used proprietary drug utilization databases available to the Agency to conduct these analyses. Detailed descriptions of the databases are included in the Appendix.

#### 2.2.1 Data Sources Used

IQVIA, National Sales Perspectives™ (NSP) database was used to determine the settings of care where olanzapine products were sold from manufacturers to the various channels of distribution in the U.S. for 2019.

IQVIA, National Prescription Audit™ (NPA) database was used to determine the estimated number of prescriptions dispensed for olanzapine and other antipsychotics from U.S. outpatient retail and long-term care pharmacies from 2016 through 2019. This database was also used to determine the top prescriber specialties for olanzapine in 2019.

The Symphony Health™ IDV (Integrated Dataverse) database was used to obtain the nationally estimated number of patients with outpatient retail pharmacy prescription claims for olanzapine or opioid containing products as well as the number of patients with concurrent olanzapine and opioid containing prescription claims from 2016 through 2019. Patient counts were stratified by patient age (<18, 18-64, and 65+ years). Patient selection was based on the presence of prescription claims using the national drug codes (NDC) for olanzapine and products containing an opioid. “Opioid containing products” (Appendix 7.7) encompass a broad category of all formulations of opioids analgesics and cough-cold products that contain an opioid.

A look back period of 180 days prior to the start of the study was applied to check for prescription claims within the study market to determine patient activity. An episode of concurrency was identified when an episode in the base group, olanzapine, overlapped with an episode in the concurrent group, opioid containing products. Episodes with overlapping days’ supply of at least 1 day from both the base group and the concurrent group during a calendar year were identified as having concurrency for that year. Our analysis did not distinguish between patients having one versus multiple concurrent episodes during a calendar year and did not capture the indication of use for these instances of concurrency.

We applied a liberal definition of concurrency by adding a grace period of one-half of the total days’ supply time window for a dispensed prescription in either the base group or the concurrent group. A grace period was applied to prescription claims to allow for the days’ supply time window to adjust for delays in prescription filling. For example, if the
total days of therapy for a claim were 30 days, a grace period of \( \frac{1}{2} \) times 30 would add 15 more days for a total of 45 days of therapy.

The Syneos Treatment Answers™ database was used to determine the top diagnoses associated with the use of olanzapine as reported by office-based physicians from January 2018 through December 2019, cumulative.

2.3 National Survey on Drug Use and Health (NSDUH)

Prevalence of opioid nonmedical use and opioid use disorder

The National Survey of Drug Use and Health (NSDUH) is an annual national survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) designed to provide nationally representative estimates of illicit as well as prescription drug nonmedical use in the general U.S. population. NSDUH uses a multistage probability sample design to provide representative state and country-level estimates for non-institutionalized residents of the U.S. who are aged 12 years and above. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey does sample people from noninstitutional group quarters like shelters, halfway houses, and college dormitories. The survey is conducted in a face-to-face manner, and during the year 2018, the interview response rate of 49% included 67,791 completed interviews. We extracted estimates of prevalence of past-year nonmedical use of prescription opioids and prevalence of past-year opioid use disorder among those 26 years and older from the most recent NSDUH report, 2018.

2.4 Review of Published Literature

Associations between bipolar disorder or schizophrenia, chronic pain, and opioid nonmedical use

To better understand the patient population potentially at elevated risk for opioid withdrawal or overdose while taking olanzapine/samidorphan, we conducted a systematic literature review of published epidemiologic studies examining the associations between

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\( ^a \) Diagnoses are expressed as "drug use mentions" which refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

\( ^b \) NSDUH’s definition of misuse (use in any way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor), aligns with the combined regulatory definitions of misuse and abuse, so we also refer to this measure as nonmedical use when describing NSDUH data.
bipolar disorder or schizophrenia and opioid nonmedical use. We searched PubMed, Embase, and Web of Science for relevant studies published after 2010, because articles within the past decade more accurately reflect current populations diagnosed with the specified psychiatric disorder or opioid use disorder. We excluded studies published outside the U.S., because substance use patterns vary widely across countries, as well as randomized clinical trials, and case studies. We included only original studies; review articles were assessed for any additional relevant, original studies that had not been identified in our search. The search string for this literature review is in appendix 7.1. Additionally, in order to understand the prevalence of chronic pain in these populations, we reviewed studies referenced by articles captured in the search described above that examined the prevalence of chronic pain diagnoses among individuals with schizophrenia or bipolar disorder. Abstracted information from included studies is in appendix 7.3.

Epidemiology of opioid overdose or precipitated withdrawal associated with use of oral naltrexone

To better understand opioid overdose or precipitated withdrawal associated with use of an oral µ-opioid receptor antagonist, we searched PubMed, Embase, and Web of Science for studies describing the epidemiology of opioid overdose or precipitated withdrawal associated with use of oral naltrexone. We excluded studies that failed to distinguish between oral and injectable naltrexone, randomized controlled trials (i.e., efficacy trials), and case studies. The search string for this literature review is in appendix 7.2. Abstracted information from included studies is in appendix 7.4.

3 REVIEW RESULTS

3.1 ASSOCIATIONS BETWEEN BIPOLAR DISORDER OR SCHIZOPHRENIA, CHRONIC PAIN, AND OPIOID NONMEDICAL USE

Studies using the National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), a cross-sectional, nationally representative survey on alcohol use disorder, drug use disorders, and comorbidities that also longitudinally follows participants, generally found an association between opioid nonmedical use\(^c\) and bipolar disorder (both for individuals diagnosed with bipolar I specifically, and individuals diagnosed with bipolar I or II).\(^3-8\) Results from this survey showed that individuals who report nonmedical opioid use at baseline have 1.7 times the odds of new bipolar diagnosis, compared to those without nonmedical opioid use;\(^5\) and individuals with bipolar disorder at baseline have 1.7 times the odds of subsequent nonmedical opioid use

\(^c\) Opioid nonmedical use in NESARC is defined as: use without a prescription or in greater amounts, more often, or longer than prescribed, or for a reason other than a doctor said you should use them.
compared to those without bipolar disorder at baseline.\textsuperscript{5} Those with opioid use disorder at baseline also have 1.5 to 1.9 times the odds of bipolar diagnosis,\textsuperscript{5,6} although those with bipolar disorder at baseline had similar odds of subsequent opioid use disorder, compared to those without bipolar disorder at baseline.\textsuperscript{5} Studies using NESARC data also found that the odds of a bipolar diagnosis increased with more severe and more recent opioid nonmedical use. For instance, participants with more frequent opioid nonmedical use had increased odds of a bipolar diagnosis as opposed to those with less frequent use.\textsuperscript{8}

NSDUH reports that the prevalence of past year opioid nonmedical use in 2018 was 3.6% and past year opioid use disorder was 0.7% for adults aged 26 and older in the U.S. A 2005 study estimated the point prevalence of opioid use disorder among individuals with bipolar disorder receiving care at a Veterans Affairs clinic at 2.7%.\textsuperscript{9} The elevated odds ratios (some of which are incidence odds ratios) reported above for individuals with nonmedical opioid use or opioid use disorder to be diagnosed with bipolar disorder, and for those with bipolar disorder to report nonmedical use or opioid use disorder, indicate that likely the prevalence of opioid nonmedical use and opioid use disorder is higher in the population with bipolar disorder as compared to the general population. Given the elevated odds ratios reported in these studies, and the estimated prevalence of nonmedical opioid use or opioid use disorder in the general population, the percentage of individuals with bipolar disorder who use opioids nonmedically may be higher than 5%, and percentage of individuals with bipolar disorder who have opioid use disorder may be in the range of 1%-3%.

Data are sparse on nonmedical opioid use and opioid use disorder in patients with schizophrenia. Some studies conducted in populations seeking treatment for substance use disorders suggest that individuals who report nonmedical substance use with no co-occurring mental health disorder are more likely to prefer opioids as compared to individuals who report substance nonmedical use with co-occurring schizophrenia, indicated by the smaller proportion of treatment-seeking individuals with schizophrenia who report a problem with opioids as opposed to the treatment-seeking population with no psychiatric disorder.\textsuperscript{10} However, older national survey data from the National Institute of Mental Health Epidemiologic Catchment Area Program (1980-1984) suggest a positive association between opioid nonmedical use and co-occurring schizophrenia.\textsuperscript{11} National survey data from NESARC also suggest that individuals with schizophrenia have more than 5 times the lifetime prevalence of opioid nonmedical use, compared to individuals with no psychiatric disorder.\textsuperscript{12}

Generally, in studies using treatment records and administrative claims data, patients with bipolar disorder had 1.7-1.9 times the odds of being diagnosed with a pain condition as compared with those without bipolar disorder, and also had higher odds (2.1) of receiving a chronic opioid prescription.\textsuperscript{13,14} Among a sample of 38,117 adults with bipolar
disorder, 10.4% were categorized as receiving a chronic opioid prescription, compared with 3.0% of their matched controls.\textsuperscript{14} Results were mixed for patients with schizophrenia regarding whether they were more or less likely to be diagnosed with a pain condition or receive a chronic opioid medication as compared to those without schizophrenia.\textsuperscript{13, 14} Although some studies showed that patients with schizophrenia were more likely to receive a diagnosis for a chronic pain condition overall, when analyses were adjusted for demographic characteristics, the odds of patients with schizophrenia receiving a chronic pain diagnosis fell below that of patients without mental illness.\textsuperscript{13, 14} It is unclear, based on the evidence presented in the studies, why patients with schizophrenia are less likely to be diagnosed with a chronic pain disorder, but a number of hypotheses are presented in the study, including: 1) difficulty in those with schizophrenia expressing experiences of pain, 2) healthcare providers interpreting patients’ reports of pain differently when they are diagnosed with schizophrenia, 3) fragmentation and inconsistent continuum of care for those diagnosed with schizophrenia.\textsuperscript{13}

\textbf{3.2 UTILIZATION PATTERNS OF OLANZAPINE AND OPIOID-CONTAINING PRODUCTS, INCLUDING CONCOMITANT USE OF THESE MEDICATIONS}

\textbf{3.2.1 Settings of Care}

In 2019, approximately 66\% of olanzapine products were distributed to outpatient retail pharmacies, followed by 31\% to non-retail pharmacies, and 3\% to mail-order/specialty pharmacies.\textsuperscript{d} Of the 31\% distributed through non-retail channels, approximately 42\% were distributed to long-term care (LTC) facilities. Therefore, our analyses focused on outpatient retail pharmacy settings and included estimates for prescriptions dispensed to LTC settings of care.

\textbf{3.2.2 Concurrency Analysis for Olanzapine and Opioid Containing Products}

Table 1 below provides national estimates of patients with prescription claims for olanzapine and opioid containing products concurrently or as individual agents, stratified by age, from U.S. outpatient retail pharmacies from 2016 to 2019. Patients receiving prescriptions dispensed for opioid containing products decreased 25\% from approximately 78 million patients in 2016 to 58 million patients in 2019. Patients receiving prescriptions dispensed for olanzapine increased 21\% from approximately 1.3 million patients in 2016 to 1.6 million patients in 2019.

In 2016, approximately 26\% (342,000 patients) of total patients with olanzapine prescription claims had concurrent prescription claims with opioid containing products.

In 2019, the proportion of patients with concurrent claims (olanzapine and opioid containing products) decreased to 21% (339,000 patients).

A lower proportion of concurrency (4%) was observed in patients <18 years of age compared to patients 18-64 years (21%) and 65 years and older (27%) in 2019 and similar patterns were observed during the entire study period.
### Table 1. National estimates of patients* who received a dispensed prescription for olanzapine and opioid containing products** concurrently or as individual agents, stratified by patient age, from U.S. outpatient retail pharmacies, 2016-2019

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th></th>
<th>2017</th>
<th></th>
<th>2018</th>
<th></th>
<th>2019</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient count</td>
<td>Concurrent patients</td>
<td>Concurrent %</td>
<td>Patient count</td>
<td>Concurrent patients</td>
<td>Concurrent %</td>
<td>Patient count</td>
<td>Concurrent patients</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1,326,683</td>
<td>342,029</td>
<td>25.8%</td>
<td>1,445,301</td>
<td>348,717</td>
<td>24.1%</td>
<td>1,506,624</td>
<td>332,486</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>70,758</td>
<td>3,160</td>
<td>4.5%</td>
<td>78,816</td>
<td>3,427</td>
<td>4.3%</td>
<td>84,072</td>
<td>3,215</td>
</tr>
<tr>
<td>18-64 years</td>
<td>1,008,163</td>
<td>262,261</td>
<td>26.0%</td>
<td>1,104,557</td>
<td>268,813</td>
<td>24.3%</td>
<td>1,154,890</td>
<td>255,625</td>
</tr>
<tr>
<td>65+ years</td>
<td>247,432</td>
<td>76,584</td>
<td>31.0%</td>
<td>261,638</td>
<td>76,459</td>
<td>29.2%</td>
<td>267,356</td>
<td>73,624</td>
</tr>
<tr>
<td>Unknown age</td>
<td>31</td>
<td>12</td>
<td>37.4%</td>
<td>42</td>
<td>8</td>
<td>19.6%</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Opioid containing products**</td>
<td>77,665,471</td>
<td>342,029</td>
<td>0.4%</td>
<td>71,731,417</td>
<td>348,717</td>
<td>0.5%</td>
<td>64,192,075</td>
<td>332,486</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>3,720,707</td>
<td>3,160</td>
<td>0.1%</td>
<td>3,317,629</td>
<td>3,427</td>
<td>0.1%</td>
<td>2,696,224</td>
<td>3,215</td>
</tr>
<tr>
<td>18-64 years</td>
<td>56,915,177</td>
<td>262,261</td>
<td>0.5%</td>
<td>52,326,303</td>
<td>268,813</td>
<td>0.5%</td>
<td>46,767,112</td>
<td>255,625</td>
</tr>
<tr>
<td>65+ years</td>
<td>17,025,392</td>
<td>76,584</td>
<td>0.4%</td>
<td>16,084,860</td>
<td>76,459</td>
<td>0.5%</td>
<td>14,725,143</td>
<td>73,624</td>
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<tr>
<td>Unknown age</td>
<td>1,545</td>
<td>12</td>
<td>0.8%</td>
<td>1,706</td>
<td>8</td>
<td>0.5%</td>
<td>1,650</td>
<td>8</td>
</tr>
</tbody>
</table>


*The patient counts are pulled and projected at each unique level of reporting. For this reason, the age breakouts may not sum to unique projected total patients.  
**Opioid containing products consist of claims for products that contain any opioids which include opioid analgesics, cough/cold products, tramadol, and combination products. (Appendix 7.7)

### 3.2.3 Prescription Data from U.S. Outpatient Retail and Long-term Care Pharmacies

Prescriptions for antipsychotic products have increased 3% from approximately 61 million prescriptions in 2016 to 64 million prescriptions in 2019 (Table 2 in Appendix 7.6). Figure 1 below and Table 3 in Appendix 7.6 show the estimated number of prescriptions dispensed for antipsychotic agents from outpatient retail and long-term care pharmacies, stratified by molecule in 2019. Of the estimated 64 million prescriptions for antipsychotic agents dispensed, olanzapine accounted for approximately 12% (7.4 million prescriptions).
Figure 1. Estimated number of antipsychotic prescriptions dispensed from U.S. outpatient retail and long-term care pharmacies stratified by active moiety*, 2019

Total Antipsychotic prescriptions dispensed in 2019: Approximately 64 million

- Quetiapine: 33% (21 million)
- Olanzapine: 12% (7 million)
- Aripiprazole: 18% (11 million)
- Haloperidol: 4% (3 million)
- Risperidone: 16% (10 million)
- *All Others: 17% (11 million)


*All Others include prescriptions for haloperidol, ziprasidone, clozapine, paliperidone, brexpiprazole, cariprazine, aripiprazole, loxapine, selpercidone, paliperidone, ziprasidone, thiothixene, pimozide, and molindone.

Figure 2 below and Table 4 in Appendix 7.6 provide the estimated number of olanzapine prescriptions dispensed from U.S. outpatient retail and long-term care pharmacies stratified by prescriber specialties in 2019. Psychiatry was the top prescriber specialty and prescribed approximately 37% of estimated prescriptions, followed by nurse practitioners/physician assistants (NP/PA) at 29%, and internal medicine at 9%. All
other specialties accounted for 9% of estimated olanzapine prescriptions dispensed in 2019.

**Figure 2. Estimated number of olanzapine prescriptions dispensed from U.S. outpatient retail and long-term care pharmacies, 2019, stratified by prescriber specialty.**

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**Total olanzapine prescriptions by prescriber specialties: Approximately 7 million**

- Psychiatry 37% (3 million)
- NP/PAs* 29% (2 million)
- Internal medicine 9% (688,000)
- Family practice 9% (487,000)
- Osteopathic medicine 7% (559,000)
- **All others 9%**

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*NP/PA: consists of nurse practitioners/physician assistants;

**All others include prescriber specialties for geriatrics, geriatric psychiatry, neurology, oncology, general practice, others, emergency medicine, pediatrics, internal/pediatrics, nephrology, cardiology, hospice & palliative medicine, physical medicine & rehab, psychology, obstetrics/gynecology, pulmonary diseases, infectious disease, general surgery, pharmacist, gastroenterology, anesthesiology, pulmonary critical care, endocrinology, addiction medicine, sleep medicine, rheumatology, pain medicine, hematology, dermatology, dentistry, clinical neurophysiology, urology, sports medicine, orthopedic surgery, nuclear medicine, general preventive medicine, critical care medicine, thoracic surgery, radiology, plastic surgery, pathology, otolaryngology, other surgery, ophthalmology, occupational medicine, neurological surgery, naturopathic doctor, clinical pharmacology, allergy, critical care surgery, podiatry, critical care pediatric, ortho surgery of spine, optometry, nutrition, medical microbiology, intern medicine-diagnostic, hepatology, genetics, dermatology-pathology, colon & rectal surgery, cardiothoracic surgery, and allergy/immunology diag lab.
3.2.4 Survey Data from Office-Based Physicians

An analysis of the top diagnoses associated with the use of olanzapine as reported by U.S. office-based physician surveys from January 2018 through December 2019 was conducted (Table 5 in Appendix 7.6). Schizophrenia was the top diagnosis associated with the use of olanzapine, accounting for 32% of total drug use mentions, followed by schizoaffective disorders at 21%, and bipolar disorder at 20% of drug use mentions.

3.3 Epidemiology of Opioid Overdose or Opioid Withdrawal Associated with Use of Oral Naltrexone

Since samidorphan is not currently marketed in the U.S., we searched the medical literature for information relating to opioid overdose or withdrawal associated with use of naltrexone. We identified four studies relating to oral naltrexone and opioid overdose or overall mortality, only one of which was conducted in the U.S. The U.S. study was a retrospective cohort study that analyzed commercial claims for individuals diagnosed with opioid use disorder who initiated treatment between 2010 and 2016. This study found that the rate of fatal or non-fatal opioid overdose among those on oral naltrexone was 6.2 overdoses per 100 person years. The overdose rate increased to 11.0 overdoses per 100 person years during the 4-week window after discontinuation of oral naltrexone. For those who had been off treatment for greater than four weeks, the overdose rate was 5.0 overdoses per 100 person years.15 A study of patients with opioid use disorder in Australia found a similar increase in overdose rate during the period following naltrexone discontinuation; the mortality rate during the 2-week post-discontinuation period was 22.1 per 100 person-years compared to 1 death per 100 person-years during treatment.16

It should be noted that the populations in these studies are comprised of patients currently undergoing treatment for opioid use disorder, and are likely to be at greater risk of opioid overdose than the general population of individuals using prescription opioids or the populations for which olanzapine/samidorphan is indicated.

In a 2017 FDA review of a bupropion/naltrexone product marketed for the indication of weight loss, 11% of patients on bupropion/naltrexone had concurrent claims for opioid products, despite their contraindication in product labeling. This concurrency analysis used national projections generated from outpatient retail dispensing claims; as patient outcome data were not available, the FDA review could not assess risk of opioid overdose in these patients. Review of postmarket cases in the FDA Adverse Event Reporting System (FAERS) and the National Poison Data System (NPDS) identified

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6 Diagnoses are expressed as "drug use mentions" which refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
adverse events potentially related to opioid withdrawal reportedly occurring when bupropion/naltrexone was used with an opioid. At the time of the review, just over two years of postmarketing data were available, yielding 69 cases in FAERS and 22 cases in NPDS. Though the majority of the cases were mild, there were a few cases of more severe events such as seizures requiring hospitalization.  

Finally, although clinical case reports exist describing naltrexone-accelerated opioid detoxification, we did not find any epidemiologic studies related to unintended, precipitated opioid withdrawal associated with single-entity oral naltrexone.

4 DISCUSSION

Olanzapine/samidorphan contains a full µ-opioid receptor antagonist. Although chronic use of opioids and opioid dependence are proposed contraindications for olanzapine/samidorphan, it is important to consider scenarios where a prescriber may be unaware of a patient’s opioid use, including when the patient is using opioids nonmedically (i.e., using them not as prescribed, for example, taking longer than directed or obtaining them from a source other than their own prescription), or if the patient has an undisclosed opioid use disorder. One safety concern is the potential for inadvertently precipitating opioid withdrawal in patients who are opioid dependent, either through medical or nonmedical chronic opioid exposure. Epidemiologic studies show an association between bipolar disorder and chronic pain conditions. In one U.S. study, percentage of patients with bipolar disorder who reported chronic opioid use was three times higher than patients without bipolar disorder.  

National survey data suggest a higher prevalence of opioid nonmedical use and opioid use disorder in people with bipolar disorder relative to the general population.  

Considering the estimated prevalence of nonmedical opioid use (3.6%) or opioid use disorder (0.7%) in the general U.S. population, the percentage of individuals with bipolar disorder who use opioids nonmedically in a given year may be greater than 5%, and the percentage of individuals with bipolar disorder who have opioid use disorder may be in the range of 1%-3%. The percentage of individuals with schizophrenia who use opioids nonmedically could be even higher, although the data on schizophrenia and nonmedical opioid use are sparse. All of these estimates are approximate, as there is not current, direct data on the prevalence of opioid use disorder among those with bipolar disorder or schizophrenia, likely due to the challenging nature of this population to study and lack of reliable measures (i.e., claims-based algorithms) of opioid use disorder that can be linked to these diagnoses. In addition, prevalence of opioid nonmedical use and opioid use disorder varies across different populations. Therefore, it is difficult to accurately estimate the percentage of individuals who might be at risk for nonmedical opioid use while on

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olanzapine/samidorphan. Nonetheless, the available data suggest that a non-trivial proportion of the indicated population could use opioids nonmedically.

A 2017 review of postmarket cases in FAERS and the NPDS identified adverse events potentially related to opioid withdrawal reportedly occurring when an approved, naltrexone-containing product (bupropion/naltrexone) was used with an opioid. These cases indicate that adverse events related to opioid withdrawal may occur when a product containing an opioid antagonist is used concurrently with opioids. However, the applicability of adverse events in this population compared to the population who may be prescribed olanzapine/samidorphan is limited due to the potential differences in the two opioid antagonists, including pharmacological differences and differences in the indicated patient populations.

Another possible scenario is a patient taking olanzapine/samidorphan who develops a severe pain condition requiring opioid analgesics. If the analgesic effect is reduced due to samidorphan’s opioid receptor antagonism, the patient could experience inadequately controlled pain and might also increase their dose in order to overcome the antagonist blockade. This could put the patient at elevated risk for opioid overdose if the samidorphan effect wanes or fluctuates, exposing the patient to a high level of unopposed opioid agonist. A recent FDA analysis of annual retail pharmacy dispensing data found that roughly one in five patients dispensed olanzapine received a concomitant prescription for an opioid analgesic. Although these data do not predict the percentage of patients taking olanzapine/samidorphan who would use opioids, they suggest that a substantial proportion of individuals prescribed olanzapine/samidorphan may at some point require opioid pain medication and be at risk for inadequate analgesia and possibly opioid overdose. A 2017 FDA review of bupropion/naltrexone indicated that 11% of patients on bupropion/naltrexone had a concurrent claim for opioid products, despite their contraindication in labeling, suggesting that despite the proposed labeling in olanzapine/samidorphan, concurrent use of opioids could occur in the patient population. Due to limitations in the data sources, the report did not distinguish the reason for this co-prescribing despite the contraindication in labeling. Moreover, the FDA review could not assess risk of opioid overdose in these patients because the concurrency analysis used national projections generated from outpatient retail dispensing claims data, and patient outcome data were not available. In addition, individuals prescribed olanzapine/samidorphan who use opioids nonmedically could be at risk for overdose if they attempt to overcome the opioid blockade.

A final scenario to consider is a patient who tapers off chronic opioids to initiate olanzapine/samidorphan, and later discontinues olanzapine/samidorphan and resumes opioid use. If these patients resume their previous opioid dose, they may be at elevated risk of opioid overdose due to loss of opioid tolerance. Epidemiologic studies suggest that patients being treated for opioid use disorder with naltrexone (an opioid receptor
antagonist) have a period of increased opioid overdose risk immediately following naltrexone discontinuation (or waning of effect, in the case of depot naltrexone).\textsuperscript{15, 16} It should be noted that these studies follow patients being treated for opioid use disorder, who are likely to be at greater risk for opioid overdose than olanzapine/samidorphan’s indicated patient population.

5 CONCLUSION

The potential safety concerns related to samidorphan’s opioid antagonist effect in various real-world settings of opioid use warrant careful consideration. These concerns include the potential for precipitated withdrawal, inadequate analgesia, and opioid overdose. The epidemiologic data suggest that a substantial subset of the indicated patient population could be at risk for one or more of these adverse events.

6 REFERENCES


APPENDIX

7.1 LITERATURE REVIEW SEARCH STRING: ASSOCIATIONS BETWEEN BIPOLAR DISORDER OR SCHIZOPHRENIA, CHRONIC PAIN, AND OPIOID NONMEDICAL USE

OR "opioid-sparing"[tw] OR "nerve block"[tw] OR "nerve blocks"[tw] OR "nerve blockade"[tw] OR "nerve blockades"[tw] OR "nerve blockades"[tw] OR "nerve blockades"[tw] OR "nerve blockade"[tw] OR "local anesthetic nerve block"[tw] OR "local anesthetic nerve block"[tw] OR "central nerve block"[tw] OR epidural[tw] OR epidurals[tw] OR "spinal anesthesia"[tw] OR "spinal anesthesia"[tw] OR "neurolytic block"[tw] OR "neurolytic blocks"[tw] OR "neonatal abstinence syndrome"[tw] OR NAS[tw] OR "neonatal opioid withdrawal syndrome"[tw] OR "amniotic fluid embolism"[tw] OR "opioid induced constipation"[tw] OR "opioid-induced constipation"[tw] OR OIC[tw] OR "enhanced recovery"[tw] OR "enhanced recovery after surgery"[tw] OR "total intravenous anesthesia"[tw] OR TIVA[tw] OR "palliative sedation"[tw] OR intrathecal[tw] OR "extracorporeal membrane oxygenation"[tw] OR ECMO[tw] NOT (animals[tw] OR animal OR "Pogona vitticeps"[tw] OR mice[tw] OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinea OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR ericetina OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa"[tw] OR ferrets OR ferret OR polecats OR polecat OR "mustela putorius"[tw] OR "guinea pigs"[tw] OR "guinea pig"[tw] OR cavia OR callithrix OR marmoseta OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbilla OR gerbils OR jird OR jirds OR meriones OR meriones OR rabbits OR rabbit OR hare OR hares OR diptera OR flies OR fly OR dipteral OR drosophila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematodes OR sipuncula OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthrhopoids OR saginus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongos OR pygmaeus OR "ongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemus OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR fowl OR owls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carp OR carps OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR barb OR mullet OR mullets OR seahorse OR seahorses OR mugil OR cernua OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR soles
Embase:


Embosc:

(bipolar OR 'manic depression' OR 'manic depression' OR 'schizophrenia' OR 'schizophrenia')

AND ("opium" OR "opium" OR "opium tincture" OR "opium tincture" OR 'paregoric' OR 'paregoric')

OR 'paregoric' OR 'morphine' OR 'morphine' OR 'kadian' OR 'kadian' OR 'morphabond' OR 'morphabond'

OR 'arymo' OR 'arymo' OR 'ms contiu' OR 'ms contiu' OR 'msir' OR 'msir'

OR 'astamorph' OR 'astamorph' OR 'astamorph' OR 'duramorph' OR 'duramorph' OR 'infumorph' OR 'infumorph'

OR 'nuprin' OR 'nuprin' OR 'nuprin' OR 'nuprin' OR 'nuprin' OR 'nuprin'

OR 'omephene' OR 'omephene' OR 'omephene' OR 'omephene' OR 'omephene' OR 'omephene'

OR 'oxydol' OR 'oxydol' OR 'oxydol' OR 'oxydol' OR 'oxydol' OR 'oxydol'

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7.2 Literature review search string: Epidemiology of opioid overdose/withdrawal associated with use of oral naltrexone

Pubmed: ("oral naltrexone" [tw] OR "naltrexone hydrochloride"[tw]) AND ("opioid"[tw]) AND ("withdrawal"[tw] OR "overdose"[tw])

Embase: (oral naltrexone' OR 'naltrexone hydrochloride') AND 'opioid' AND ('withdrawal' OR 'overdose')

Web of Science: ("oral naltrexone" OR 'naltrexone hydrochloride') AND 'opioid' AND ('withdrawal' OR 'overdose')
7.3 ABSTRACTED ARTICLES FROM LITERATURE REVIEW ON ASSOCIATIONS BETWEEN BIPOLAR DISORDER OR SCHIZOPHRENIA, CHRONIC PAIN, AND OPIOID NONMEDICAL USE
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Dataset/Study Design</th>
<th>Study Population</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birgenheir, 2013</td>
<td>Dataset: Administrative data extracted from Veterans' Health Treatment Records. Study design: Cross-sectional</td>
<td>All individuals who received health care in the Veterans Affairs (VA) system during 10/1/2017-9/30/2018.</td>
<td>Seven specific pain conditions examined (based on ICD-9 codes from electronic medical record) were arthritis, back pain, chronic non-cancer pain, migraine headaches, tension and other headaches, psychogenic, and neuropathic. Clinical diagnoses were based on ICD-9 codes recorded by healthcare providers and included schizophrenia and bipolar disorders. Disorders were coded hierarchically into mutually exclusive categories such that schizophrenia&gt;bipolar disorder&gt;depression to eliminate diagnostic overlap. Descriptive statistics were first used to determine the overall prevalence of chronic pain conditions in those with schizophrenia or bipolar disorder. Next, a series of logistic regression analyses examined unadjusted and adjusted associations of serious psychiatric diagnoses with pain conditions.</td>
<td>Patients with schizophrenia comprised 1.8% of the total population. In unadjusted analyses, compared to patient without schizophrenia, bipolar, or depression, patients with schizophrenia were more likely to report any pain condition (OR=1.21), as well as every pain condition, arthritis (OR=1.16), back pain (OR=1.37), chronic pain (OR=2.84), migraine (OR=1.46), other headache (OR=2.02), psychogenic (OR=4.56), neuropathic (OR=1.09). In adjusted analyses compared with patients without schizophrenia, bipolar, or depression, patients with schizophrenia were less likely to have any pain condition (OR=0.91), as well as arthritis (OR=0.93), and neuropathic pain (OR=0.94), but continued to have higher odds of diagnoses of chronic (OR=2.10), migraine (OR=1.13), other headache (OR=1.46), and psychogenic (OR=2.72) pain conditions. Patients with bipolar disorder comprised 1.9% of the total population. In unadjusted analyses, compared to patients without schizophrenia, bipolar, or depression, patients with bipolar disorder were over twice as likely to have any pain condition (OR=2.17), and every specific pain condition, arthritis (OR=1.75), back pain (OR=2.47), chronic pain (OR=5.43), migraine (OR=4.67), other headache (OR=3.46), psychogenic (OR=10.17), and neuropathic (OR=4.9). In adjusted analyses, patients with bipolar disorder had significantly higher odds of having any pain condition (OR=1.83), as well as every specific pain condition, arthritis (OR=1.59), back pain (OR=1.93), chronic non-cancer pain (OR=4.03), migraine (OR=2.75), other headache (OR=2.34), psychogenic (OR=6.24), and neuropathic pain (OR=1.50).</td>
<td>(-) Sample includes only patients in VA system, not nationally representative (-) Recognition of pain condition depends on doctor diagnoses. (-) Large sample size could overrepresent statistical significance of findings</td>
</tr>
<tr>
<td>Chiapelli, 2018</td>
<td>Dataset: Treatment Episode Dataset - Dischart (TEDS-D) 2011 Study Design: Cross-sectional</td>
<td>Part of a national census of annual discharges from substance abuse treatment facilities.</td>
<td>Chi square tests to compare proportions of individuals reported as having problems with either alcohol, cocaine/crack, marijuana, heroin, or non-heroin opioid. Addition treatment population. Patients with schizophrenia were compared to patients with depressive disorders, bipolar disorders, and treatment seeking population with no specifically reported psychotic, depressive, or bipolar diagnosis.</td>
<td>Proportion of patients reporting problem with non-heroin opiates: Schizophrenia: 7.2% Bipolar: 17.3% Population with no psychotic, depressive, or bipolar diagnosis: 14.8% Proportion of patients reporting problem with heroin: Schizophrenia: 5.1% Bipolar: 7.0% Population with no psychotic, depressive, or bipolar diagnosis: 18.2%</td>
<td>(-) Cross sectional design does not allow for understanding of temporal causality (-) Treatment seeking population only (-) No information on polysubstance</td>
</tr>
<tr>
<td>Grant, 2016</td>
<td>Dataset: National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), Wave 3 2012-2013 (nationally representative) Study design: Cross-sectional</td>
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<tr>
<td>NESARC participants: Non-institutionalized adult population of the United States</td>
<td>Diagnosis based on national institute on alcohol abuse and alcoholism alcohol use disorder and associated disabilities interview schedule DSM-5 (AUDADIS-5). Odds ratios of psychiatric comorbidity on drug use disorder obtained from multivariable logistic regressions adjusted for sociodemographic characteristics and all other substance use and psychiatric disorders.</td>
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<tr>
<td>Adjusted odds ratio (95% CI) for bipolar I disorder among those with past-year drug use disorder:</td>
<td>Adjusted odds ratio (95% CI) for bipolar I disorder among those with lifetime drug use disorder:</td>
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<tr>
<td>Any drug use disorder: 1.5 (1.06-2.05)</td>
<td>Any drug use disorder: 1.4 (1.14-1.74)</td>
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<tr>
<td>Mild drug use disorder: 1.0 (0.65-1.64)</td>
<td>Mild drug use disorder: 0.8 (0.55-1.29)</td>
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<tr>
<td>Moderate to severe drug use disorder: 1.8 (1.22-2.65)</td>
<td>Moderate to severe drug use disorder: 1.6 (1.29-2.02)</td>
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<tr>
<td>Adjusted odds ratio (95% CI) for schizotypal disorder among those with past-year drug use disorder:</td>
<td>Adjusted odds ratio (95% CI) for schizotypal disorder among those with lifetime drug use disorder:</td>
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<tr>
<td>Any drug use disorder: 1.5 (1.18-1.87)</td>
<td>Any drug use disorder: 1.5 (1.23-1.73)</td>
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<tr>
<td>Mild drug use disorder: 1.4 (1.04-1.87)</td>
<td>Mild drug use disorder: 1.3 (0.98-1.63)</td>
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<tr>
<td>Moderate to severe drug use disorder: 1.6 (1.15-2.09)</td>
<td>Moderate to severe drug use disorder: 1.5 (1.27-1.86)</td>
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<table>
<thead>
<tr>
<th>Iyiewuare, 2017</th>
<th>Dataset: Authors surveyed patients entering federally qualified health clinic (FQHC) in Los Angeles (LA) Study Design: Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>15,723 adults visiting the FQHC from June 3, 2014 to January 15, 2016.</td>
<td>Presence of mental illness determined via self-report/hospitalization records, diagnosis of substance abuse was assessed via NIDA-modified version of the World Health Organization’s Alcohol, Smoking, and Substance Involvement screening test version 3.1. Chi square tests were used to compare characteristics.</td>
</tr>
<tr>
<td>Of the clinic population, 9.6% had ever been diagnosed with bipolar disorder, and 1 3% had ever been diagnosed with schizophrenia or schizoaffective disorder. Of the study sample, composed of those with substance misuse, 31.9% had ever been diagnosed with bipolar disorder, and 13.2% had ever been diagnosed with schizophrenia or schizoaffective disorder.</td>
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</table>

- Small, single institution study in LA, not nationally representative
- Treatment seeking population only
- Cross sectional design does not allow for understanding of temporal causality
<p>| Kerridge 2015 | Dataset: National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), Wave 3 2012-2013 (nationally representative) | Study design: Cross-sectional | NESARC participants: Non-institutionalized adult population of the United States | Diagnosis based on National Institute on Alcohol Abuse and Alcoholism's Alcohol Use and Associated Disabilities Interview Schedule 5 (AUDADIS-5) in order to measure DSM-5 disorders. Authors used multiple logistic regression to derive adjusted odds ratios for association between non-medical prescription opioid use/disorder and sociodemographic characteristics controlling for all others. Logistic regressions of psychiatric comorbidity with Nonmedical use/disorder controlled for sociodemographic characteristics and other substance use/psychiatric disorders. | Adjusted odds ratio (95% CI) of 12-month nonmedical prescription opioid use and bipolar I: Men: 1.35 (0.82-2.22) Women: 1.22 (0.77-1.93) | Adjusted odds ratio (95% CI) of lifetime nonmedical prescription opioid use and bipolar I: Men: 1.06 (0.81-1.39) Women: 1.15 (0.85-1.55) | Adjusted odds ratio (95% CI) of 12-month nonmedical prescription opioid use disorder and bipolar I: Men: 1.86 (0.99-3.49) Women: 1.61 (0.71-3.68) | Adjusted odds ratio (95% CI) of lifetime nonmedical prescription opioid use disorder and bipolar I: Men: 1.61 (1.02-2.54) Women: 1.44 (0.85-2.42) | Adjusted odds ratio (95% CI) of 12-month nonmedical prescription opioid use and schizotypal: Men: 1.55 (1.19-2.01) Women: 1.27 (0.89-1.79) | Adjusted odds ratio (95% CI) of lifetime nonmedical prescription opioid use and schizotypal: Men: 1.39 (1.09-1.78) Women: 1.34 (1.03-1.74) | Adjusted odds ratio (95% CI) of 12-month nonmedical prescription opioid use disorder and schizotypal: Men: 1.43 (0.88-2.32) Women: 1.45 (0.75-2.81) | Adjusted odds ratio (95% CI) of lifetime nonmedical prescription opioid use disorder and schizotypal: Men: 1.72 (1.18-2.50) Women: 1.09 (0.75-1.58) | (-) Does not cover homeless population, might underestimate prevalence of opioid nonmedical use and mood disorders (-) Cross-sectional nature of data does not allow for understanding of temporal causality of drug use and psychological disorder |</p>
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Dataset</th>
<th>Study Design</th>
<th>Methodology</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidof, 2018</td>
<td>Dataset: Data collected by authors from new admissions to Addiction Treatment Services, a methadone-assisted treatment program in Baltimore, Maryland. Study design: Cross-sectional</td>
<td>208 new admissions to Addiction Treatment services in Baltimore. All participants were opioid-dependent and referred from the Baltimore needle exchange program. Recruited from August 2010-April 2015. Exclusion criteria: cognitive impairment.</td>
<td>Participants were interviewed by research staff with battery of tests including SCID I for lifetime and current diagnosis of many DSM IV-TR Axis I substance use and non-substance use psychiatric disorders, and SCID II for diagnoses of personality disorder. Patients underwent urine drug testing.</td>
<td>Prevalence of bipolar I and schizophrenia in the population of opioid-dependent individuals was 12% and 0%, respectively.</td>
<td>Limited sample, not nationally representative convenience sample. Cross-sectional nature of data does not allow for understanding of temporal causality of drug use and psychological disorder. Treatment seeking population only. Data are self-report.</td>
</tr>
<tr>
<td>Martins, 2011</td>
<td>Dataset: National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), Wave 1 (2001-2002). Study design: Cross-sectional</td>
<td>NESARC participants: Non-institutionalized adult population of the United States, 43,093 individuals. Diagnosis based on National Institute on Alcohol Abuse and Alcoholism's Alcohol Use and Associated Disabilities Interview Schedule 5 (AUDADIS-5) in order to measure DSM-5 disorders. Data analyzed using weighted proportions, 95% CIs, and weighted logistic regression models to generate odds ratios (Or) adjusted for socio-demographic characteristics.</td>
<td>Weighted proportion of respondents with schizophrenia who have lifetime use (95% CI) of: Heroin: 2.6% (0-8.4-4.3%) Opioids: 17.6% (12.4%-22.8%) Weighted proportion of respondents with schizophrenia who have lifetime abuse only (95% CI) of: Heroin: 1.0% (-0.2%-2.3%) Opioids: 1.7% (-1.2%-4.6%) Weighted proportion of respondents with schizophrenia who have lifetime dependence only (95% CI) on: Heroin: NA Opioids: 0.1% (-0.1%-0.3%) Weighted proportion of respondents with schizophrenia who have lifetime abuse and dependence (95% CI) on: Heroin: 1.1% (-0.1%-2.3%) Opioids: 3.6% (0.4%-6.8%)</td>
<td>Very small number of individuals with schizophrenia in the NESARC study. Large 95% CIs that often cross zero. Unable to create ORs for schizophrenia.</td>
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Martins, 2012  

**Dataset:** National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), Wave 1 (2001-2002) and Wave 2 (2004-2005) (nationally representative)  

**Study Design:** Longitudinal cohort study  

**NESARC participants:** Non-institutionalized adult population of the United States  

Diagnosis based on national institute on alcohol abuse and alcoholism alcohol use disorder and associated disabilities interview schedule DSM-4 (AUDADIS-4). Two sets of nested logistic regression analyses examined whether nonmedical prescription opioid use and disorders due to this use predict incident mood/anxiety disorders at follow-up at wave 2.  

1) Demographics were included in the models as covariates. 2) Controlled for baseline substance use variables, baseline comorbid anxiety/mood disorders. A second set of nested logistic regression analyses examined whether mood/anxiety disorders at baseline predict incident nonmedical prescription opioid use and disorders at wave 2.  

1) Controlling for demographics and 2) including a binary variable for baseline mood/anxiety disorder. Models also controlled for baseline other substance use.  

Among those with baseline lifetime nonmedical prescription opioid use, controlling for demographics and other substance use, adjusted odds ratio (95% CI) for:  

- Any mood disorder: 1.8 (1.4-2.3)  
- Bipolar I disorder: 1.7 (0.8-3.6)  
- Bipolar disorder: 2.0 (1.1-3.7)  

(Reference is absence of nonmedical prescription opioid use at baseline)  

Among those with baseline lifetime abuse/dependence due to nonmedical use, controlling for demographics and other substance use, adjusted odds ratio (95% CI) for:  

- Any mood disorder: 1.5 (0.9-2.5)  
- Bipolar I disorder: 1.9 (0.5-6.9)  
- Bipolar disorder: 2.6 (1.0-6.8)  

(Reference is absence of baseline lifetime abuse/dependence due to nonmedical use)  

Among those with baseline any mood disorder, controlling for demographics, comorbid mood/anxiety disorders, other substance use, adjusted odds ratio (95% CI) for:  

- Incident nonmedical prescription opioid use: 1.6 (1.3-2.0)  
- Incident abuse/dependence secondary to nonmedical use: 2.1 (1.5-3.0)  

(Reference is absence of baseline mood disorder)  

Among those with baseline bipolar I disorder, controlling for demographics, comorbid mood/anxiety disorders, other substance use, adjusted odds ratio (95% CI) for:  

- Incident nonmedical prescription opioid use: 1.7 (1.1-2.6)  
- Incident abuse/dependence secondary to nonmedical use: 1.1 (0.5-2.3)  

(Reference is absence of baseline bipolar I disorder)  

Among those with baseline bipolar disorder, controlling for demographics, comorbid mood/anxiety disorders, other substance use, adjusted odds ratio (95% CI) for:  

- Incident nonmedical prescription opioid use: 2.0 (1.4-2.8)  
- Incident abuse/dependence secondary to nonmedical use: 1.4 (0.7-2.5)  

(Reference is absence of baseline bipolar disorder)  

---  

(-) Most respondents past the median age of psychopathology onset, resulting in lower incidence rate over follow-up than expected in general population.  

(-) Data on nonmedical use and psychopathology self-report  

(-) Cox2 inhibitors included in opioid category in wave 2 of NESARC possibly inflating rates of opioid nonmedical use in wave 2 compared to wave 1.  

(-) Does not cover homeless population, might underestimate prevalence of opioid nonmedical use and mood disorders.
<p>| Owen-Smith, 2020 | Dataset: Electronic medical records from 13 mental health research network sites within a large integrated health care delivery system. Study design: Case-control. | Cases: adults aged 18-70 years with diagnosis of major depressive disorder, bipolar disorder, or schizophrenia including schizoaffective disorder documented at least 2x by mental healthcare provider with continuous health plan membership through 2015 and 2016. Exclusions: any cancer or metastatic cancer diagnoses. Controls identified using same criteria with no documented mental illness diagnoses. Controls matched based on age, sex, and Medicare status using random sampling. Matching 1:2 for schizophrenia and 1:1 for bipolar disorder and major depressive disorder. | For initial bivariate models, authors used t-tests for continuous variables and chi squared tests for categorical data. Multivariate analyses were conducted to evaluate odds of receiving a chronic pain-related diagnosis and the odds of receiving opioids, controlling for age, sex, Medicare status, race/ethnicity, income, medical comorbidities, healthcare utilization, and chronic pain diagnosis. Chronic opioid prescription was considered to be dispensing that covered at least 70 days in any 90 day period or 6+ dispensings in 2016. | Patients with major depressive disorder vs. matched controls: Any pain: 62.4% vs. 39.8% Chronic opioid use: 10.1% vs. 2.4% Patients with bipolar disorder vs. matched controls: Any pain: 61.5% vs. 40.3% Chronic opioid use: 10.4% vs. 3.0% Patients with schizophrenia vs. matched controls: Any pain: 47.2% vs. 42.0% Chronic opioid use: 6.5% vs. 5.0% Adjusted odds ratio (95% CI) of receiving a chronic pain diagnosis among individuals with vs. without mental illness diagnosis: Major depressive disorder: 1.90 (1.85-1.95) Bipolar disorder: 1.71 (1.66-1.77) Schizophrenia: 0.86 (0.82-0.90) Adjusted odds ratio (95% CI) of receiving a chronic opioid prescription among individuals with vs. without mental illness diagnosis: Major depressive disorder: 2.59 (2.44-2.75) Bipolar disorder: 2.12 (1.97-2.28) Schizophrenia: 1.00 (0.91-1.11) | (-) Treatment seeking population only (-) Largely insured sample, may not be representative of the population under study (-) Opioid prescription data based on dispensing. |</p>
<table>
<thead>
<tr>
<th>Saha, 2016</th>
<th>Dataset: National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), Wave 3 2012-2013 (nationally representative) Study design: Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NESARC participants:</strong> Non-institutionalized adult population of the United States</td>
<td><strong>Diagnosis based on national institute on alcohol abuse and alcoholism alcohol use disorder and associated disabilities interview schedule DSM-5 (AUDADIS-5). Adjusted odds ratios were calculated from multiple logistic regressions to indicate association between nonmedical prescription opioid use/disorder and psychiatric comorbidity controlling for all other sociodemographic characteristics and psychiatric disorders.</strong></td>
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<td><strong>Adjusted odds ratios (95% CI) of 12-month opioid use disorder and comorbid disorder:</strong> Bipolar I: 1.73 (1.09-2.74) Schizotypal personality disorder: 1.44 (0.94-2.22) (Reference group, absence of 12-month opioid use disorder)</td>
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<td></td>
<td><strong>Adjusted odds ratios (95% CI) of lifetime opioid use disorder and comorbid disorder:</strong> Bipolar I: 1.50 (1.07-2.12) Schizotypal personality disorder: 1.35 (1.01-1.80) (Reference group, absence of lifetime opioid use disorder)</td>
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<td></td>
<td>(-) Study was cross-sectional, no information on temporal causality chronology of opioid nonmedical use/disorder and mood disorders</td>
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<td>(-) Most respondents past the median age of psychopathology onset, resulting in lower incidence rate over follow-up than expected in general population.</td>
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<td>(-) Does not cover homeless population, might underestimate prevalence of opioid nonmedical use and mood disorders</td>
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</table>
Scheps, 2011


Study design: Longitudinal cohort

NESARC participants: Non-institutionalized adult population of the United States
Analyses split NESARC participants into four groups based on wave 1 data:
1) no life-time non-medical use of controlled prescription medication (NUPM) and no history of outcome psychopathology
2) life-time NUPM but no history of outcome psychopathology
3) no life-time NUPM with a previous episode of outcome psychopathology
4) life-time NUPM and a previous episode of outcome psychopathology

Diagnosis based on national institute on alcohol abuse and alcoholism alcohol use disorder and associated disabilities interview schedule DSM-4 (AUDADIS-4). Authors used logistic regression to examine the risk for the onset of an outcome disorder in wave 2 by history of NUPM in wave 1. Authors performed a second set of analyses in those with history of psychopathology at wave 1 to examine risk for the recurrence of the previous diagnosis during the follow-up and examine the risk for onset of new psychopathology during the follow-up.

Reported adjusted odds ratio, adjusting for socio-demographic factors and wave 1 personality disorder diagnostic status.

Adjusted odds ratio (95% CI) among those with any NUPM and no history of psychopathology for diagnosis of:
Bipolar (I or II): 2.61 (2.03-3.36), p<0.001
(Reference group, no history of NUPM and no history of psychopathology)

Adjusted odds ratio (95% CI) among those with past-year non-medical use of prescription medication and no history of psychopathology for diagnosis of:
Bipolar (I or II): 2.81 (2.47-3.21), p<0.0001
(Reference group, no past-year non-medical opioid use and no history of psychopathology)

Adjusted odds ratio (95% CI) among those with past-year non-medical opioid use for recurrence of measured diagnoses:
Bipolar (I or II): 1.76 (1.28-2.42), p=0.0005
(Reference group, no past-year opioid nonmedical use)

Adjusted odds ratio (95% CI) among those with past-year non-medical opioid use and past psychopathology for onset of new psychopathology:
Bipolar (I or II): 1.29 (1.05-1.59), p=0.014
(Reference group, no past-year non-medical opioid use with past psychopathology)

(-) Most respondents past the median age of psychopathology onset, resulting in lower incidence rate over follow-up than expected in general population.

(-) Data on nonmedical use and psychopathology self-report

(-) Temporal causality of psychopathology and non-medical use unclear, did not study effect of psychopathology on substance use

(-) Does not cover homeless population, might underestimate prevalence of opioid nonmedical use and mood disorders
<p>| Schepis, 2013 | Dataset: National Epidemiological Survey on Alcoholism and Related Conditions (NESARC), Wave 1 (2001-2002) and Wave 2 (2004-2005) (nationally representative) | NESARC participants: Non-institutionalized adult population of the United States | Diagnosis based on national institute on alcohol abuse and alcoholism alcohol use disorder and associated disabilities interview schedule DSM-4 (AUDADIS-4). Multivariate logistic regression used to examine effect of past-year nonmedical use on 1) development of new diagnosis in wave 2 in those with past diagnosis of another psychiatric illness and 2) recurrence of psychopathology at wave 2 for those with history of disorder but without a current episode at wave 1. Participants with no history of psychopathology were not included. | Adjusted odds ratio (95% CI) of incidence of bipolar (I or II) psychopathology in individuals using opioids nonmedically: Non-users: 0.74 (0.63-0.87) Weekly/daily users: 2.12 (1.52-2.96) (Reference group is monthly or less users) Adjusted odds ratio (95% CI) of recurrence of bipolar (I or II) psychopathology in individuals using opioids nonmedically: Non-users: 0.66 (0.45-0.96) Weekly/daily users: 1.15 (0.54-2.44) (Reference group is monthly or less users) | - Most respondents past the median age of psychopathology onset, resulting in lower incidence rate over follow-up than expected in general population. - Data on nonmedical use and psychopathology self-report - Cox2 inhibitors included in opioid category in wave 2 of NESARC possibly inflating rates of opioid nonmedical use in wave 2 compared to wave 1. - Does not cover homeless population, might underestimate prevalence of opioid nonmedical use and mood disorders |</p>
<table>
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<tr>
<th>Yoon, 2014</th>
<th>Dataset: 2010 Nationwide Inpatient Sample (NIS), largest all-payer inpatient-care database in the United States (nationally representative) Study design: Cross-sectional</th>
</tr>
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<tbody>
<tr>
<td>Patients captured in the nationwide inpatient sample &gt;=12 years of age, with valid report of sex. 6,686,905 discharges.</td>
<td>Diagnosis codes in NIS based on ICD-9 codes. Descriptive estimates produced with 95% CI. Cross-tabulation was used to examine how substance use disorders and mood/anxiety disorders are distributed across unintentional alcohol and/or drug poisonings and all hospitalizations. Strength of association between alcohol/drug poisoning and psychiatric disorders was further quantified by the adjusted prevalence ratio (or risk ratio) of cases with a particular type of psychiatric disorder as compared with those without it estimated from three Poisson regression models: 1) unintentional alcohol poisoning only, 2) unintentional drug poisoning only, 3) unintentional alcohol and drug poisoning, with no alcohol or drug poisoning as reference. To understand relative risk of specific drug poisoning, eight Poisson regression models corresponding to eight categories of drugs with &quot;other drugs&quot; as reference, were used to compare relative risk of associated specific psychiatric disorder for being poisoned by specific drug type among cases of unintentional drug poisoning.</td>
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<td>Among hospitalizations for unintentional drug poisoning in men, 10.8% (95% CI: 10.1%-11.4%) occurred among men with bipolar disorder. Among hospitalizations for unintentional drug poisoning in women, 14.1% (95% CI: 13.3%-14.8%) occurred among women with bipolar disorder. Adjusted risk ratio for unintentional drug poisoning only among those with bipolar disorder (reference group those with no alcohol/drug poisoning) was 2.09 (95% CI 2.03-2.15) for men and 3.53 (95% CI 3.44-3.62). Adjusted risk ratio for unintentional drug poisoning related to illicit opioids among those with bipolar disorder (reference group &quot;other drugs&quot;) was 0.94 (0.87-1.02) for men and 1.00 ((0.93-1.08) for women. Adjusted risk ratio for unintentional drug poisoning related to prescription opioids among those with bipolar disorder (reference group &quot;other drugs&quot;) was 0.99 (0.94-1.05) for men and 1.05 (1.01-1.10) for women.</td>
<td>Among hospitalizations for unintentional drug poisoning, 10.8% (95% CI: 10.1%-11.4%) occurred among those with bipolar disorder. Hospitalizations with drug poisoning might be more likely to be screened for psychological disorder. Treatment seeking individuals only</td>
</tr>
<tr>
<td>Zhao, 2020</td>
<td>Dataset: Data collected by authors from participants during computer-assisted interviews. Study design: Cross-sectional.</td>
</tr>
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## 7.4 Abstracted Articles from Literature Review on Epidemiology of Opioid Overdose Associated with Use of Oral Naltrexone

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Dataset/Study Design</th>
<th>Study Population</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations</th>
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<tr>
<td>Darke, 2019</td>
<td>Dataset: Australia’s national coronial information system (NCIS). Linked coroner’s report, autopsy report, police and toxicology reports.</td>
<td>Closed cases on NCIS between January 2000 and December 2017 where decedent was being treated with naltrexone. Included if there was evidence of prescribing of oral preparations within the previous month, a depot injection within the previous month, or an implant within the previous 6 months. Cases where naltrexone was prescribed for alcohol dependence with no evidence of opioid use were not included.</td>
<td>For normally distributed variables, mean and standard deviation and range was reported, otherwise medians and ranges were reported. Mann-Whitney U tests were used for comparison of morphine concentrations in those with and without naltrexone present at the time of death.</td>
<td>There were 74 fatalities while using naltrexone. Accidental opioid toxicity accounted for 59 (79.7%) of cases. Of the 74 fatalities, 41 (55.4%) were maintained on oral naltrexone, 24 (32.4%) were maintained on implant naltrexone, 4 (5.4%) were an unknown naltrexone formulation, and 5 (6.8%) were using oral naltrexone for detoxification. Among the naltrexone fatalities, 28.4% tested positive for naltrexone (21: oral 3, implant 12, detoxification 2, unknown 4), 25.7% tested negative (19: oral 16, implant 2, detoxification 1) and 45.9% were not tested (34: oral 22, implant 10, detoxification 2). Among those screened for naltrexone, the drug was present in the blood or urine of 52.5% (15.8% of oral maintenance cases, 85.7% of implant cases).</td>
<td>(-) Not conducted in the US (-) Case series, no information on prevalence (-) Large amount of cases with unknown formulation</td>
</tr>
<tr>
<td>Author, year</td>
<td>Dataset/Study Design</td>
<td>Study Population</td>
<td>Methods</td>
<td>Results</td>
<td>Limitations</td>
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<tr>
<td>Fellows-Smith 2011</td>
<td>Dataset: Data linkage between Western Australia deaths register and recorded admissions to the Perth Naltrexone Clinic and community-based methadone program. Study Design: Open-label sequential cohort study</td>
<td>3,617 patients undergoing opioid pharmacotherapy at the Perth naltrexone clinic and community-based methadone substitution program from 1998-2000 (2,520 methadone, 1,097 for naltrexone).</td>
<td>Mortality rates were calculated as cumulative all-cause deaths per 1,000 person years. Naltrexone and methadone decedents from all causes were compared with decedents from their age-matched controls.</td>
<td>Mortality rate was 2.6% per year for oral naltrexone treatment. Mortality rate for oral naltrexone group was 26.28 per 1,000 person years, and mortality rate due to opioid toxicity was 17.98 per 1,000 person years. Mortality rate per 1,000 person years for methadone patients was 7.37 (95% CI: 5.00-9.75) compared with 26.28 (95% CI: 17.95-34.61) for oral naltrexone. Relative risk compared with age-matched control was 3.38 (95% CI: 2.29-4.47) for methadone, and 12.05 (95% CI: 8.23-15.87) for oral naltrexone. Of the 37 deaths in the methadone cohort, 21 were accidental opioid poisoning. Of the 38 deaths in the oral naltrexone cohort, 26 were accidental opioid poisoning. Relative risk of death from opioid toxicity was 4.3 times greater following oral naltrexone treatment.</td>
<td>(•) Demographics different between naltrexone vs. methadone cohort, naltrexone cohort younger, male, single, unemployed (•) Patients likely self-selected treatment, likely confounding by indication</td>
</tr>
<tr>
<td>Gibson, 2007</td>
<td>Dataset: National Coronial Information System of Australia Study design: Retrospective cohort study</td>
<td>Mortality from naltrexone, buprenorphine, and methadone in Australia</td>
<td>Number of deaths related to naltrexone, buprenorphine, and methadone was determined by keyword search of the National Coronial Information System of Australia between 2000-2003. Mortality rates were calculated using (a) a crude rate of deaths per 1000 treatment episodes and (b) a stratified death rate of deaths per 100 person-years at high or low risk of death. High-risk was considered to be deaths where the date of death was recorded as being within 2 weeks after cessation of naltrexone treatment episode or in the first week of methadone or buprenorphine treatment. Low-risk period was defined as deaths during naltrexone treatment or after the first week of methadone or buprenorphine treatment.</td>
<td>During the 2000-2003 study period, there were 282 methadone, 1 buprenorphine, and 32 oral naltrexone-related deaths. Crude-estimated mortality rate was 2.7 deaths per 1000 episodes for methadone, 0.02 per 1000 treatment episodes for buprenorphine, and 10.1 per 1000 treatment episodes for naltrexone. Naltrexone subjects had 3.7 (95% CI: 2.5-5.2) times the mortality risk compared to methadone subjects. Methadone treatment was associated with a mortality rate of 3.0 per 100 person-years during the high-risk period and 0.34 per 100 person-years during the low-risk period. Naltrexone was associated with a mortality rate of 22.1 per 100 person-years during the period of high risk, and 1.0 per 100 person-years during the period of low risk. Naltrexone subjects 2 weeks post-treatment (high-risk period) had 7.4 times the risk of dying than methadone subjects in their first week of treatment (high-risk period). This risk was highly significant (95% CI: 4.6-11.5). Naltrexone subjects during treatment (low-risk period) had 2.8 times the risk of dying than methadone subjects in the post-induction treatment period (low-risk period). This risk approaches significance (95% CI: 1.3-5.7)</td>
<td>(•) Unclear crossover between cases: if naltrexone episodes were being used for detoxification and then patients would be moved to methadone/buprenorphine, in which case this period might be more high risk (•) Different definitions of high-risk and low-risk periods for naltrexone vs. MAT treatments might have made non-comparable categories (•) Mortality was not overdose specific</td>
</tr>
<tr>
<td>Author, year</td>
<td>Dataset/Study Design</td>
<td>Study Population</td>
<td>Methods</td>
<td>Results</td>
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<tr>
<td>Hulse, 2005</td>
<td>Dataset: Data collected from West Australian Health Services Research Linked Database and the emergency department information system. Study design: Retrospective cohort study.</td>
<td>Population of Western Australia who interacted with health services or the emergency department. Cohort consisted of 361 heroin dependent persons who received naltrexone implant treatment for heroin dependence between January 2001-December 2002. A sub-cohort composed of those who had been on oral naltrexone pre-implant consisted of 174 people.</td>
<td>Overdoses were defined and grouped via ICD-10 codes. For oral naltrexone sub-analysis, ICD-9 CM codes were inspected to identify opioid, sedative, and other substance poisoning for admission prior to July 1999.</td>
<td>146 oral naltrexone sub-cohort who had 6-month interval between oral naltrexone and implant and who were in the hospital admission database. Of these 146 people, in the 6 months pre-oral treatment, there were seven opioid overdoses (prevalence n=6 persons, 4.1%), compared with nine overdoses (prevalence n=8 persons, 5.5%) in the 6-months post-oral treatment and zero in the 6-months post-implant.</td>
<td>ICD-9 codes used for oral naltrexone outcomes because of early time point. These are individuals with heroin use disorder, likely on the severe end of addiction spectrum. Medication compliance may be different between medication for opioid use disorder and anti-psychotic. Unclear if overdose was due to illicit or prescription opioids. Outside the US.</td>
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<tr>
<td>Kelty, 2012</td>
<td>Dataset: Linked data from Australian institute of health and welfare and the national death index for patients under study. Study design: Retrospective cohort study.</td>
<td>1467 patients treated with oral naltrexone, 1701 patients treated with implant naltrexone, and 688 patients treated with both at a community not-for-profit drug treatment clinic in Australia between 1997-2009.</td>
<td>Crude mortality rates were calculated two ways: 1) initial treatment, which consisted of separating patients into oral vs implant. For patients who moved groups, initial treatment only was considered and data collected after initial treatment was not included, and 2) all treatment, which consisted of separating patients into oral vs. implant, but patients who underwent both therapies were included in each treatment category. Patients years were calculated from commencement of one treatment to the second treatment, and fatality was assigned to the most recent treatment. Age-specific, age-standardized, gender-specific and cause-specific mortality were calculated for patients using the all-treatment approach.</td>
<td>Crude overall mortality rates for patients on oral naltrexone was 8.78 per 1000 patient years. During the first four months following treatment, mortality rates in oral naltrexone patients were significantly higher than in patients treated with implant naltrexone (26.28 deaths per 1000 patient years in oral compared with 7.34 deaths per 1000 patient years in implant group. All treatment approach.) In subsequent time-periods, there was only a significant difference in the 8-12 month time-period. Rate of opioid overdose mortality rate in oral naltrexone group dropped to &lt;5 deaths per 1000 patient years. Mortality associated with opioid overdose high in young age group for oral patients, not seen for implant group. Mortality rate not significantly different between initial treatment groups for oral vs. implant, but crude mortality for all-treatment groups was higher for oral naltrexone than implant (8.78 deaths per 1000 patient years for oral (95% CI: 7.38-10.17), 6.59 deaths per 1000 patient years for implant (95% CI: 5.13-8.06.)</td>
<td>Length of follow up longer for oral naltrexone. Oral treatments performed tended to be earlier in time than implant treatments. Often patients were treated with oral naloxone first then implant, not often treated with implant and then switched to oral.</td>
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<tr>
<td>Author, year</td>
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<td>Morgan, 2019</td>
<td>Dataset: Truven Health Analytics MarketScan Commercial Claims Database (MarketScan) Study Design: Retrospective cohort study</td>
<td>Patients in MarketScan from 2010-2016 with 1) evidence of diagnosis of opioid use disorder (OUD) based on ICD-9 or ICD-10 codes in medical claims; 2) prescription of naltrexone or buprenorphine.</td>
<td>Outcome measures: Overdose events based on ICD-9 and 10 codes on an inpatient or outpatient medical claim. Measured whether the individual was currently receiving each of the three medications (extended-release naltrexone (XR-NTX), oral naltrexone, and buprenorphine) in a given week. Calculated person-time accrued on each medication and time spent on no medication. Outpatient prescription drug data determined date on which individuals filled prescriptions and days’ supply. Used a four week window for recent discontinuation. Individuals began contributing follow-up time at their initial medication for opioid use disorder, after having not received medication for opioid use disorder for three months. In time to event analysis, individuals ceased contributing when they experienced an overdose or were censored at the end of the study period or exit from commercial insurance plan. Analyses: Calculated unadjusted overdose rate for each treatment status (current XR-NTX, current oral naltrexone, current buprenorphine, or no current treatment). Calculated incidence rate of overdose per 100 person years and 95% CI. Developed a Cox hazards model on a weekly timescale to predict time from medication for opioid use disorder initiation to first opioid related overdose as a function of medication type, both currently prescribed and recently discontinued within the previous four weeks, controlling for demographic factors.</td>
<td>Cohort included 46,846 individuals with 72,215 person years. Buprenorphine: 40,441 persons with 29,628 person years, oral naltrexone: 7782 persons with 1617 person years, and injectable naltrexone: 1386 persons with 390 person years. There were 1805 individuals who experienced 2755 opioid-related overdoses during the study period. Unadjusted opioid-related overdose rate (95% CI) per 100 person years during treatment: Not on treatment: 4.98 (4.79-5.22) overdoses per 100 person years; Buprenorphine: 2.08 (1.94-2.26) overdoses per 100 person years; XR-NTX: 3.85 (2.31-6.37) overdoses per 100 person years; Oral naltrexone: 6.18 (5.08-7.52) overdoses per 100 person years. Unadjusted opioid-related overdose rate (95% CI) per 100 person years during 4-week discontinuation periods: Buprenorphine: 3.86 (3.36-4.23) overdoses per 100 person years; XR-NTX: 10.46 (6.40-17.06) overdoses per 100 person years; Oral naltrexone: 10.96 (8.82-13.63) overdoses per 100 person years; Adjusted hazard ratio opioid-related overdose rate (95% CI) per 100 person years; During treatment compared to no treatment: Buprenorphine: 0.40 (0.35-0.46) XR-NTX: 0.74 (0.42-1.31) Oral naltrexone: 0.93 (0.71-1.22). Adjusted hazard ratio opioid-related overdose rate (95% CI) during discontinuation per 100 person years compared to no treatment: Buprenorphine: 1.08 (0.91-1.28) XR-NTX: 1.50 (0.83-2.73) Oral naltrexone: 1.15 (0.84-1.57)</td>
<td>(-) Only commercially insured population (-) Only opioid overdoses captured in claims (-) Differences in demographics for treatment populations</td>
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<tr>
<td>Author, year</td>
<td>Dataset/Study Design</td>
<td>Study Population</td>
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<td>Robertson, 2018</td>
<td>Dataset: Linkage between department of mental health and addiction services (DMHAS), department of social services Medicaid program, and department of corrections, department of public safety, and judicial branch. Study Design: Retrospective cohort study</td>
<td>Persons aged 18 years and older having a recorded diagnosis of schizophrenia spectrum disorder, bipolar disorder, major depression, a recorded diagnosis of moderate to severe opioid dependence, at least one night spent in Connecticut jail or prison during 2002-2009 and having engaged in community-based treatment for opioid dependence between 2003-2008. 8736 adults.</td>
<td>Index date for pharmacotherapy group was the first observed outpatient opioid-dependence pharmacotherapy episode. For those treated with buprenorphine or naloxone, started counting maintenance episodes on 8th day, to isolate maintenance from possible detoxification. For comparison group, index treatment episode was first observed episode of outpatient substance abuse treatment without pharmacotherapy or outpatient mental health treatment if accompanied by opioid dependence diagnosis. Outcomes measured: inpatient mental health treatment, inpatient substance abuse treatment, visits to ED or crisis care provider.</td>
<td>Of 4,800 opioid-dependent adults with serious mental illness in Connecticut public behavioral system, 267 were treated with Naltrexone for index treatment episode. Demographics and clinical characteristics of opioid-dependent adults with severe mental illness in Connecticut Naltrexone cohort: Schizophrenia: 54 (20.22%)Bipolar: 98 (36.70%)Depression: 115 (43.07%)Oral naltrexone group had no difference from comparison group (no pharmacotherapy) in terms of ER/crisis center use 0.86 (0.68-1.08) but a reduction in use for substance abuse mental health services 0.61 (0.47-0.79) and 0.61 (0.43, 0.89), respectively.</td>
<td>(-) Opioid withdrawal/overdose not a specific outcome (-) Odds ratios are in comparison to comparison group with opioid dependence diagnosis without treatment, but not clear overall amount of health care utilization due to opioid dependence in cohort of patients with serious mental illness on naltrexone (-) Naltrexone adherence unclear</td>
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<tr>
<td>Tait, 2008</td>
<td>Dataset: Clinic records from not-for-profit community-based treatment service for heroin dependence in Perth, Western Australia. West Australia Data Linkage System (WADLS)Study Design: Retrospective cohort study</td>
<td>People from West Australia who received naltrexone implants between January 2001 and December 2002 and who could be followed in the WADLS. Cohort consisted of 174 people who sequentially entered treatment for heroin dependence initially using oral naltrexone and who later received sustained release implant naltrexone.</td>
<td>Study assessed hospital admission in the 6-month period prior to and following self-reported first heroin use. First period of dependent heroin use was designated as the 6-month period before oral naltrexone treatment where a diagnosis of DSM-IV dependence was required for treatment entry. The second period of dependent heroin use was designated as the 6-month period before sustained release naltrexone treatment where a diagnosis of DSM-IV dependence was also required for treatment entry.</td>
<td>For patients during the oral naltrexone period, 92/130 were admitted to the hospital for any reason. There were 56 mental health opioid related admissions and seven admissions for opioid overdose.</td>
<td>(-) Heroin use was self-report (-) Oral naltrexone was used as a mechanism of transfer to naltrexone implant, could be a time of fluctuation (-) Small cohort (-) Unclear which drugs were involved in overdoses</td>
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7.5 DATABASE DESCRIPTIONS

**IQVIA, National Sales Perspectives™, Retail and Non-Retail**

IQVIA, National Sales Perspectives™ (NSP) measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of eaches and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Estimates provided in this review are national estimates, but statistical tests were not performed to determine whether statistically significant changes occurred over time or between products; therefore, all changes over time should be considered approximate. In addition, these results cannot be validated through medical chart reviews.

**IQVIA National Prescription Audit™**

The IQVIA National Prescription Audit™ (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 59,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 93% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 71 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month. We focused our prescription count analyses from outpatient retail pharmacy prescription claims. Therefore, these estimates may not apply to other settings of care in which these products are used, such as mail-order pharmacies or specialty pharmacies.

**IDV® (Integrated Dataverse)**

IDV (Integrated Dataverse) from Symphony Health contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 280 million unique prescription patients of with an average of 5 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9/10 diagnosis history of which nearly 180 million prescription drug patients are linked to a diagnosis. The overall sample represents over 65,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

We focused our concurrency analyses from outpatient retail pharmacy prescription claims. Therefore, these estimates may not apply to other settings of care in which these products are used, such as mail-order pharmacies or specialty pharmacies. Furthermore, the methodologies used to assess concurrent use of olanzapine and products containing opioids were quite broad. Prescription stockpiling was not accounted for and we were not able to ascertain if the same practitioner had prescribed both olanzapine and products containing opioids. Additionally,
assumptions are made when examining concurrency, such as (a) the patient takes each dispensed prescription as indicated, and (b) the days' supply for a prescription accurately reflects how the patient is actually taking the prescription. Prescriptions with the instructions of "as needed" will tend to have a pharmacist-assigned days' supply that assumes the patient will take the maximum dose possible. This may underestimate the length of time that these 'as needed' prescriptions will actually last for a patient and thereby underestimate the true duration of therapy.

**Syneos Health Research & Insights, LLC., Treatment Answers™**

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the United States. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Diagnoses obtained from physician survey data are expressed as "drug uses" which refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. The survey data provide insight into the prescriber intent, but are not necessarily linked to dispensed prescriptions. Moreover, the absence of a mention of a drug of interest for use in association with a diagnosis does not necessarily indicate that physicians did not mention the drug during the study period; drug use mentions may have occurred on an unreported day and may not get captured. Further, the prevalence of the disease of interest should be considered when drawing inferences. Rare diseases or diseases for which patients rarely seek medical attention generally produce lower estimates or mentions of use.
### Table 2. Estimated number of antipsychotic prescriptions dispensed from U.S. outpatient retail and long-term care pharmacies, 2016-2019, annually

<table>
<thead>
<tr>
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<th>2016</th>
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<th>2018</th>
<th>2019</th>
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<tbody>
<tr>
<td>Antipsychotics</td>
<td>61,398,002</td>
<td>59,827,126</td>
<td>61,481,996</td>
<td>63,497,680</td>
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### Table 3. Estimated number of antipsychotic prescriptions dispensed from U.S. outpatient retail and long-term care pharmacies stratified by active moiety\textsuperscript{*}, 2019

<table>
<thead>
<tr>
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<th>2019</th>
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<tbody>
<tr>
<td></td>
<td>TRx (N)</td>
<td>Share (%)</td>
</tr>
<tr>
<td>Grand Total</td>
<td>63,497,680</td>
<td>100%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>21,038,080</td>
<td>33.1%</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>11,434,719</td>
<td>18.0%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>10,157,606</td>
<td>16.0%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7,432,978</td>
<td>11.7%</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2,774,382</td>
<td>4.4%</td>
</tr>
<tr>
<td>All Others*</td>
<td>10,659,915</td>
<td>16.8%</td>
</tr>
</tbody>
</table>

* All Others include prescriptions for lurasidone, ziprasidone, clozapine, paliperidone, brexipiprazole, cariprazine, asenapine, loxapine, iloperidone, pimavanserin, thiothixene, pimozide, and molindone.

### Table 4. Estimated number of olanzapine prescriptions dispensed from U.S. outpatient retail and long-term care pharmacies, 2019, stratified by prescriber specialty

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<thead>
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<tr>
<td></td>
<td>TRx (N)</td>
<td>Share (%)</td>
</tr>
<tr>
<td>Grand Total</td>
<td>7,328,678</td>
<td>100%</td>
</tr>
<tr>
<td>PSYCHIATRY</td>
<td>2,781,445</td>
<td>37%</td>
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<tr>
<td>NP/PAs*</td>
<td>2,149,701</td>
<td>29%</td>
</tr>
<tr>
<td>INTERNAL MEDICINE</td>
<td>687,896</td>
<td>9%</td>
</tr>
<tr>
<td>FAMILY PRACTICE</td>
<td>663,375</td>
<td>9%</td>
</tr>
<tr>
<td>OSTEOPATHIC MEDICINE</td>
<td>487,333</td>
<td>7%</td>
</tr>
<tr>
<td>All Others*</td>
<td>558,928</td>
<td>9%</td>
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</table>

* All others include prescriber specialties for geriatrics, geriatric psychiatry, neurology, oncology, general practice, others, emergency medicine, pediatrics, internal/pediatrics, nephrology, cardiology, hospice & palliative medicine, physical medicine & rehab, psychology, obstetrics/gynecology, pulmonary diseases, infectious disease, general surgery, pharmacist, gastroenterology, anesthesiology, pulmonary critical care, endocrinology, addiction medicine, sleep medicine, rheumatology, pain medicine, hematology, dermatology, dentistry, clinical neurophysiology, urology, sports medicine, orthopedic surgery, nuclear medicine, general
preventive medicine, critical care medicine, thoracic surgery, radiology, plastic surgery, pathology, otolaryngology, other surgery, ophthalmology, occupational medicine, neurological surgery, naturopathic doctor, clinical pharmacology, allergy, critical care

Table 5. Diagnoses (ICD-10) associated with the use of olanzapine as reported by office-based physician surveys, January 2018- December 2019, cumulative

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>January 2018- December 2019</th>
<th>Uses (000)</th>
<th>Share (%)</th>
<th>95% Confidence Interval (000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Olanzapine</td>
<td></td>
<td>5,869</td>
<td>100.0%</td>
<td>5,364-6,374</td>
</tr>
<tr>
<td>F20 Schizophrenia</td>
<td></td>
<td>1,846</td>
<td>31.5%</td>
<td>1,563-2,130</td>
</tr>
<tr>
<td>F25 Schizoaffective disorders</td>
<td></td>
<td>1,250</td>
<td>21.3%</td>
<td>1,017-1,483</td>
</tr>
<tr>
<td>F31 Bipolar disorder</td>
<td></td>
<td>1,192</td>
<td>20.3%</td>
<td>965-1,420</td>
</tr>
<tr>
<td>F32 Major depressive disorder, single episode</td>
<td></td>
<td>258</td>
<td>4.4%</td>
<td>152-364</td>
</tr>
<tr>
<td>R44 Oth symptoms and signs w general sensations and perceptions</td>
<td></td>
<td>196</td>
<td>3.3%</td>
<td>103-288</td>
</tr>
<tr>
<td>F29 Unsp psychosis not due to a substance or known physiol cond</td>
<td></td>
<td>189</td>
<td>3.2%</td>
<td>99-280</td>
</tr>
<tr>
<td>F33 Major depressive disorder, recurrent</td>
<td></td>
<td>174</td>
<td>3.0%</td>
<td>87-260</td>
</tr>
<tr>
<td>F43 Reaction to severe stress, and adjustment disorders</td>
<td></td>
<td>120</td>
<td>2.1%</td>
<td>48-192</td>
</tr>
<tr>
<td>F41 Other anxiety disorders</td>
<td></td>
<td>101</td>
<td>1.7%</td>
<td>35-167</td>
</tr>
<tr>
<td>F23 Brief psychotic disorder</td>
<td></td>
<td>74</td>
<td>1.3%</td>
<td>18-131</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>468</td>
<td>8.0%</td>
<td>326-611</td>
</tr>
</tbody>
</table>

7.7 **Drug Utilization Opioid Containing Products (includes all formulations)**

ACETAMINOPHEN WITH CODEINE  
ACETAMINOPHEN/CAFF/DIHYDROCOD  
AMMON CHL/PE/HCOD/PYR/CP/PHDM  
AMMON CHL/PHENYLEPH HCL/COD/CP  
AMMON CHL/PHENYLEPHRINE/COD/CP  
ASPIRIN/CAFFEIN/DIHYDROCODEINE  
ASPIRIN/CODEINE PHOSPHATE  
BENZHYDROCODONE/ACETAMINOPHEN  
BROMPHENIRA/PSEUDOEPHED/CODEINE  
BROMPHENIRAM/PE/DIHYDROCODEINE  
BROMPHENIRAMINE/CODEINE PHOS  
BROMPHENIRAMINE/PE/CODEINE  
BROMPHENIRAMINE/P-EPH/CODEINE  
BROMPHENRM/PSEUDOEPH/DIHYDROCD  
BUPRENORPHINE  
BUPRENORPHINE HCL  
BUPRENORPHINE HCL/NALOXONE HCL  
BUTALBIT/ACETAMIN/CAFF/CODEINE  
BUTORPHANOL TARTRATE  
CARISOPRODOL/ASPIRIN/CODEINE  
CHLORCYCLI/PSEUDOEPHED/CODEINE  
CHLORCYCLIZ/PHENYLEPH/CODEINE  
CHLORCYCLIZINE HCL/CODEINE PH  
CHLORCYCLIZINE/CODEINE  
CHLOR-MAL/CODEINE/ACETAMINOPHN  
CHLORPHEN/PSEUDOEPHED/CODEINE  
CHLORPHENIRAMINE/CODEINE PHOS  
CHLORPHENIRAMINE/PE/CODEINE  
CODEINE PHOS  
CODEINE PHOS/ASA/ACETAMINOPHEN  
CODEINE PHOS/ASA/CAFFEIN/BUTAL  
CODEINE PHOS/APAP  
CODEINE PHOS/BR-DPHA HCL  
CODEINE PHOS/CARISOPRODOL/ASA  
CODEINE PHOS/PYRIL MAL  
CODEINE PHOSPHATE  
CODEINE PHOSPHATE/APAP  
CODEINE PHOSPHATE/APAP/BUTALB  
CODEINE PHOSPHATE/ASPIRIN  
CODEINE PHOSPHATE/BR-DPHA HCL
CODEINE PHOSPHATE/GUAIFENESIN
CODEINE PHOSPHATE/PYRILAMINE
CODEINE POLI/CHLORPHENIR POLIS
CODEINE SULFATE
CODEINE/ACETAMINOPHEN/BUTALB
CODEINE/BUTALBITAL/ASA/CAFFEIN
CODEINE/CALCIUM IODIDE
CODEINE/CARISOPRODOL/ASPIRIN
CODEINE/IODINATED GLYCEROL
CODEINE/PROMETAZINE HCL
DEXBROMPHENIRAMINE/PSE/CODEINE
DEXCHLORPHEN/PHENYLEPH/CODEINE
DEZOCINE
DHCODEINE BT/ACETAMINOPHN/CAFF
DIHYDROCODEINE/ASPIRIN/CAFFEIN
DIHYDROCODEINE/GUAIFENESIN
DIPHENHYDRAMIN/PE/CODEINE PHOS
FENTANYL
FENTANYL CITRATE
FENTANYL CITRATE/PF
FENTANYL CITRATE-0.9 % NACL/PF
FENTANYL HCL
FENTANYL/BUPIVACAINE/NS/PF
FENTANYL/ROPIVACAINE/NS/PF
GUAIFEN/CODEINE PHOS/CP
GUAIFEN/HYDROCOD BIT/PHENINDA
GUAIFEN/HYDROCODONE/BR-PHENIR
GUAIFEN/HYDROCODONE/PHENINDA
GUAIFEN/PE HCL/PPA/COD/BPM
GUAIFEN/PE/PHENYLPROP/COD/BPM
GUAIFEN/PE/PHENYLPROP/HCOD/PNM
GUAIFEN/P-EPHE HCL/COD/CP
GUAIFEN/P-EPHE HCL/COD/TRIPRO
GUAIFEN/P-EPHE HCL/DIHY-COD
GUAIFEN/P-EPHE HCL/HCOD/CP
GUAIFEN/PHENYLEPHRINE/COD/CP
GUAIFEN/PHENYLEPHRINE/PPA/HCOD
GUAIFEN/PPA HCL/HCOD/PYRIL/PNM
GUAIFEN/PPA HCL/HCOD/SAL-AMIDE
GUAIFENESIN/CODEINE PHOS
GUAIFENESIN/CODEINE PHOSPHATE
GUAIFENESIN/HYDROCOD BIT
GUAIFENESIN/HYDROCODONE
GUAIFENESIN/HYDROCODONE BIT
GUAIFENESIN/P-EPHE HCL/COD
GUAIFENESIN/P-EPHED HCL/HCOD
GUAIFENESIN/PHENYLEPHRINE/COD
GUAIFENESIN/PHENYLEPHRINE/HCOD
GUAIFENESIN/PPA HCL/CODEINE
HYDROCODONE BIT/HOMATROPINE
HYDROCODONE BIT/ASPIRIN
HYDROCODONE BIT/CHLOR-MAL
HYDROCODONE BIT/HOMATROP ME-BR
HYDROCODONE BIT/HOMATROPINE
HYDROCODONE BITARTRATE
HYDROCODONE BITARTRATE/APAP
HYDROCODONE TANNATE/CHLOR-TAN
HYDROCODONE/ACETAM/DIET.SUP.11
HYDROCODONE/ACETAMINOPHEN
HYDROCODONE/CHLORPHEN POLIS
HYDROCODONE/CHLORPHEN P-STIREX
HYDROCODONE/CHLORPHENIRAMINE
HYDROCODONE/CHLOR-POLI
HYDROCODONE/CPM/PSEUDOEPHED
HYDROCODONE/IBUPROFEN
HYDROCODONE/PSEUDOEPHED/GUAIF
HYDROMORPHONE HCL
HYDROMORPHONE HCL IN 0.9% NACL
HYDROMORPHONE HCL IN WATER/PF
HYDROMORPHONE HCL/0.9% NACL/PF
HYDROMORPHONE HCL/NS
HYDROMORPHONE HCL/PF
HYDROMORPHONE/BUPIV/0.9NACL/PF
HYDROMORPHONE/ROPIV/SOD CHL/PF
IBUPROFEN/OXYCODONE HCL
KG/COD/PROMETH/SODIUM CIT
KG/SOD CIT(EXP)/COD/PROMETH
KG/SOD CIT(EXP)/PE/COD/PROMETH
KG/SODIUM CIT/COD/PROMETH
LEVOMETHADYL ACETATE HCL
LEVORPHANOL TARTRATE
MEPERIDINE HCL
MEPERIDINE HCL IN 0.9 % NACL
MEPERIDINE HCL IN 0.9% NACL/PF
MEPERIDINE HCL/ACETAMINOPHEN
MEPERIDINE HCL/PF
MEPERIDINE HCL/PROMETH HCL
METHADONE HCL
METHADONE IN 0.9 % SOD.CHLORID
MORPHINE SULFATE
MORPHINE SULFATE IN 0.9 % NAACL
MORPHINE SULFATE LIPOSOMAL/PF
MORPHINE SULFATE/0.9% NAACL/PF
MORPHINE SULFATE/D5W
MORPHINE SULFATE/D5W/PF
MORPHINE SULFATE/NALTREXONE
MORPHINE SULFATE/NORMAL SALINE
MORPHINE SULFATE/PF
MORPHINE/BIS SS/KAO/PECT
NALBUPHINE HCL
NH4CL/PE HCL/HCOD/PYR/CP/PHDM
NH4CL/PE HCL/PPA/COD/PYRIL/PNM
OPIUM TINCTURE
OPIUM/ASPIRIN/CAFFEINE
OPIUM/BELLADONNA ALKALOIDS
OPIUM/KAOLIN/PECTIN
OPIUM/KAOLIN/PECTIN/BELLADONNA
OXYCODONE HCL
OXYCODONE HCL/ACETAMINOPHEN
OXYCODONE HCL/ASPIRIN
OXYCODONE HCL/OXYCODON TER/ASA
OXYCODONE MYRISTATE
OXYCODONE/ASPIRIN
OXYMORPHONE HCL
P/EPHED/CODEINE/ACETAMINOPH/GG
PAREGORIC
PE HCL/PPA HCL/HCOD/PYRIL/PNM
PE/CODEINE/PHENIR/SODIUM CIT
PE/HYDROCODONE/BROMPHEN TANNTS
PE/HYDROCODONE/DEXBROMPHENIRMN
PE/HYDROCODONE/DEXCHLOR TANNTS
PE/P-EPHEDRINE/HCOD/PYRIL/CP
PE/PPA HCL/DIHY-COD/CP
PE/PPA HCL/HCOD/PYRIL/PHENIR
PE/PPA/HCOD/PYRIL/PHENIR
PE-CODEINE-ACETAMINOPHEN-GUAIF
PENTAZOCINE HCL/ACETAMINOPHEN
PENTAZOCINE HCL/ASPIRIN
PENTAZOCINE HCL/NALOXONE HCL
PENTAZOCINE LACTATE
P-EPD TAN/HYDROCODONE TANNATE
P-EPHED HCL/COD PHOS/TRIPROL
P-EPHED HCL/COD/CHLORPHENIR
P-EPHED HCL/CODEINE PHOSPHATE
P-EPHED HCL/CODEINE/GUAIFEN
P-EPHED HCL/DHCOD/EINE BT/CP
P-EPHED HCL/HCOD/ BT/CARBINOX
P-EPHED HCL/HYDROCOD/BIT
P-EPHED HCL/HYDROCOD/ BIT/CP
P-EPHED HCL/HYDROCODONE
P-EPHED HCL/HYDROCODONE BT
P-EPHED HCL/HYDROCODONE/ BPM
P-EPHED HCL/HYDROCODONE/CP
P-EPHED HCL/HYDROCODONE/TRIPRO
PHENYLEPH HCL/HYDROCOD BIT/CP
PHENYLEPH/CODEINE/ACETAMIN/CP
PHENYLEPH/DIHYDROCOD/EINE/GUAIF
PHENYLEPH/HYDROC/ODON/ACETAMN/CP
PHENYLEPHRINE HCL/HYDROCODONE/PROMETH
PHENYLEPHRINE HCL/HYDROCODONE/PYRIL
PHENYLEPHRINE HCL/CODEINE
PHENYLEPHRINE HCL/DIHYDROCOD/BT
PHENYLEPHRINE HCL/HYDROCODONE
PHENYLEPHRINE/COD/CP/POT IOD
PHENYLEPHRINE/CODEINE/GUAIFEN
PHENYLEPHRINE/DHCOD/EINE BT/CP
PHENYLEPHRINE/HCOD/ BT/CARBINOX
PHENYLEPHRINE/HCOD/ BT/PYRIL/CP
PHENYLEPHRINE/HCOD TAN/DPHA
PHENYLEPHRINE/HYDROCOD/ BIT/CP
PHENYLEPHRINE/HYDROCODONE/BPM
PHENYLEPHRINE/HYDROCODONE/CP
PHENYLEPHRINE/HYDROCODONE/D-CP
PHENYLEPHRINE/HYDROCODONE/DPHA
PHENYLEPHRINE/HYDROCODONE/PYR
PHENYLEPHRINE/PPA HCL/COD/CP
PHENYLPROP HCL/COD/BR-PHENIR
PHENYLPROP HCL/HYDROCOD/ BIT
POT GUAIAOCO/HYDROCOD/ BIT
POT GUAIAOCO/HYDROCODONE BIT
POT GUAIAOCO/P-EPHED HCL/HCOD
PPA HCL/CODEINE/BR-PHENIR
PPA HCL/HYDROCODONE BIT
PPA HCL/HYDROCODONE BITARTRATE
PROMETHAZINE HCL/CODEINE
PROMETHAZINE/PHENYLEPH/CODEINE
PROPOXYPHENE HCL
PROPOXYPHENE HCL/ACETAMINOPHEN
PROPOXYPHENE HCL/ASA/CAFFEINE
PROPOXYPHENE NAP/ACETAMINOPHEN
PROPOXYPHENE NAPSYL
PROPOXYPHENE NAPSYLATE
PSEUDOEPH/HYDROCOD/BROMPH TANS
PSEUDOEPH/HYDROCODON/CP TANNS
PSEUDOEPHED/COD/CHLORPHENIR
PSEUDOEPHED/CODEINE/GUAIFEN
PSEUDOEPHED/CODEINE/TRIPROLIDN
PSEUDOEPHED/HYDROCODONE
PSEUDOEPHEDRINE HCL/CODEINE
PSEUDOEPHEDRINE/COD/TRIPROL
PYRIL MA/PE/CODEINE PHOS
PYRIL MAL/PSEUDOEPHED/CODEINE
PYRILAM/PHENYLE/DIHYDROCODEINE
SUFENTANIL CITRATE
TAPENTADOL HCL
TERPIN HYDRATE/CODEINE
TRAMADOL HCL
TRAMADOL HCL/ACETAMINOPHEN
TRAMADOL/GLUCOSAMINE