

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213378Orig1s000**

**213378Orig2s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## Joint Supervisory Memo

<b>Date</b>	25 May 21
<b>From</b>	Valerie Amspacher, PharmD—Cross-Discipline Team Lead Tiffany R Farchione, MD—Director, Division of Psychiatry Eric Bastings, MD—Deputy Director, Office of Neuroscience
<b>Subject</b>	Summary Review
<b>NDA/BLA # Supp #</b>	213378
<b>Proprietary / Established (USAN) names</b>	Lybalvi (olanzapine and samidorphan)
<b>Dosage forms / strength</b>	Tablets 5 mg olanzapine/10 mg samidorphan 10 mg olanzapine/10 mg samidorphan 15 mg olanzapine/10 mg samidorphan 20 mg olanzapine/10 mg samidorphan
<b>Proposed Indication(s)</b>	<ol style="list-style-type: none"> <li>1. Schizophrenia in adults</li> <li>2. Bipolar I disorder in adults</li> <li>3. Acute treatment of manic and mixed episodes as monotherapy and as maintenance monotherapy treatment</li> <li>4. Adjunct to valproate or lithium in the treatment of manic or mixed episodes</li> </ol>
<b>Action</b>	Approval

### 1. Introduction to Review

This NDA resubmission seeks approval for Lybalvi (olanzapine/samidorphan) tablets, CII at 5 mg olanzapine/10 mg samidorphan, 10 mg olanzapine/10 mg samidorphan, 15 mg olanzapine/10 mg samidorphan and 20 mg olanzapine/10 mg samidorphan strengths. In the first review cycle, the Agency identified drug product manufacturing facility deficiencies as well as drug product process deficiencies. As a result, a Complete Response Letter (CRL) was issued on November 13, 2020. The application was otherwise considered approvable by all disciplines; however, agreement on final labeling was not reached during the initial review cycle. This review will focus only on new information submitted to resolve the deficiencies stated in the CRL and the outstanding labeling issues.

### 2. Complete Response

The CRL cited objectionable conditions at a manufacturing facility and noted that satisfactory resolution (e.g., preapproval inspection or adequate facility responses addressing these conditions) of these objectionable conditions would be required. The CRL also noted that the drug product manufacturer failed to establish (b) (4)

### 3. CMC

The Office of Pharmaceutical Quality (OPQ) team concluded the following:

- General product quality considerations  
All drug quality issues, including [REDACTED] (b) (4)  
have been resolved. All disciplines recommend approval.
- Facilities review/inspection  
Facilities are adequate.
- Other notable issues (resolved or outstanding)  
N/A

### 4. Labeling

Unresolved issues from the first review cycle included language related to samidorphan's opioid antagonist activity. Specifically, the label for this product includes a contraindication for patients who are using opioids or undergoing acute opioid withdrawal. The label also includes Warnings and Precautions describing the risk that samidorphan may precipitate opioid withdrawal in patients who are dependent on opioids, and the vulnerability to life-threatening opioid overdose in patients who try to overcome samidorphan's opioid blockade, or in patients with a history of chronic opioid use who discontinue Lybalvi and attempt to resume a previously tolerated opioid dosage. [REDACTED] (b) (4)

### 5. Conclusions and Recommendations

The concerns outlined in the CRL have been resolved and OPQ recommends approval for this application based on drug substance, drug product, process/facilities and biopharmaceutics reviews. We will issue an approval letter for this application.

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/s/  
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VALERIE R AMSPACHER  
05/25/2021 01:36:45 PM

TIFFANY R FARCHIONE  
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ERIC P BASTINGS  
05/26/2021 11:38:45 AM

**Clinical Review Memo**

<b>From</b>	Cathy Southammakosane, MD, Medical Officer, Division of Psychiatry (DP) Bernard Fischer, MD, Deputy Director and Cross-Discipline Team Leader (CDTL), DP
<b>Subject</b>	Clinical Review Memo
<b>NDA/BLA # and Supplement#</b>	NDA 213378
<b>Applicant</b>	Alkermes, Inc.
<b>Date of Submission</b>	December 1, 2020
<b>PDUFA Goal Date</b>	June 1, 2021
<b>Proprietary Name (code name)</b>	Lybalvi (ALKS 3831)
<b>Established or Proper Name</b>	Olanzapine/samidorphan
<b>Dosage Form(s) and strengths</b>	Oral tablet
<b>Applicant Proposed Indication(s)/Population(s)</b>	Original 1: Treatment of schizophrenia (adults) Original 2: (b) (4) bipolar I disorder (adults)
<b>Applicant Proposed Dosing Regimen(s)</b>	Olanzapine 5 mg/Samidorphan 10 mg once daily; Olanzapine 10 mg/Samidorphan 10 mg once daily; Olanzapine 15 mg/Samidorphan 10 mg once daily; Olanzapine 20 mg/Samidorphan 10 mg once daily
<b>Recommendation on Regulatory Action</b>	Approve
<b>Recommended Indication(s)/Population(s)</b>	Original 1: Treatment of schizophrenia (adults) Original 2: (b) (4) bipolar I disorder (adults)
<b>Recommended Dosing Regimen(s)</b>	Olanzapine 5 mg/Samidorphan 10 mg once daily; Olanzapine 10 mg/Samidorphan 10 mg once daily; Olanzapine 15 mg/Samidorphan 10 mg once daily; Olanzapine 20 mg/Samidorphan 10 mg once daily

Alkermes Inc Pharmaceuticals has resubmitted this 505(b)(2) NDA with new molecular entity (NME) for olanzapine/samidorpham for the treatment of schizophrenia and of bipolar I disorder, manic or mixed episodes and maintenance. Olanzapine is an approved atypical antipsychotic; samidorphan is an NME mu opioid receptor antagonist intended to mitigate olanzapine-associated weight gain. The original NDA was submitted on November 15, 2019, and received a complete response on November 13, 2020, secondary to findings related to a manufacturing facility. The clinical review completed at the time of original NDA submission recommended approval based upon antipsychotic efficacy and weight gain mitigation safety findings (see Appendix 1). No new clinical information was included with this resubmission. Therefore, there is no clinical efficacy or safety data for review, and the clinical recommendation is unchanged.

At the time of this review, the Prescribing Information is under negotiation with the Applicant. The following clinical recommendations for changes to the proposed label have been made to the Applicant:

- *Dosage and Administration*: The section (b) (4) was re-titled for clarity (b) (4) and was moved to Section 2.1 given its importance. Details were also modified (1) clarifying that Lybalvi is contraindicated with concomitant opioid use and (2) specifying the recommendation to delay initiation of Lybalvi based upon type of opioid use. Additionally, in the section *Administration Information*, bedtime dosing was deemed unnecessary and removed.
- *Contraindications*: Language was modified to broaden Lybalvi contraindication with concomitant opioid use and in patients undergoing acute opioid withdrawal.
- *Warnings and Precautions*:
  - Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Incidence of death in elderly patients with dementia-related psychosis in olanzapine clinical trials was added for consistency with the olanzapine label.
  - Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: That Lybalvi is not approved for the treatment of patients with dementia-related psychosis was added to align with more current class labeling.
  - (b) (4) and *Vulnerability to Life-Threatening Opioid Overdose*: As inherently different issues, these sections were modified into distinctly independent warnings and precautions. Additionally, *Vulnerability to Life-Threatening Opioid Overdose* was further subsectioned, also to reflect inherently different issues.
    - (b) (4) The opioid-free interval prior to initiation of Lybalvi was modified in consideration of the pharmacokinetic characteristics of the respective opioid (i.e., short-acting versus long-acting).

- *Vulnerability to Life-Threatening Opioid Overdose*: Further guidance was detailed for emergency situations in which a patient taking Lybalvi may require opioid treatment.
- *Drug Interaction, Effect of Lybalvi on Other Drugs*: Verbiage was modified to clarify risk for opioid withdrawal in opioid-dependent patients. Additionally, the opioid-free interval based upon the pharmacokinetic characteristics of the respective opioid (i.e., short-acting versus long-acting) prior to initiation of Lybalvi was added.
- [REDACTED] (b) (4)
- *Clinical Studies*:
  - Figure 3 was edited for a more accurate description: The preceding statement [REDACTED] (b) (4) [REDACTED] (b) (4) was deleted, and the title was modified to Change from Baseline PANSS Total Score by Time (Week) in Patients with Schizophrenia.
  - Figure 4 was similarly re-titled.
- *Patient Counseling Information*:
  - [REDACTED] (b) (4) This section was deleted to align with more current class labeling.
  - *Precipitation of Opioid Withdrawal and Risk of Opioid Overdosage*: These sections were edited to align with the Warnings and Precautions section.
  - *Neuroleptic Malignant Syndrome, Tardive Dyskinesia, Orthostatic Hypotension and Syncope, Leukopenia/Neutropenia, Potential for Cognitive and Motor Impairment, Concomitant Medication, and Body Temperature Dysregulation*: These sections were revised to align with more current class labeling.

## Appendix 1

### Conclusions and Recommendations

ALKS 3831 was studied at approved olanzapine dosages 10 to 20 mg and a fixed 10 mg samidorphan dose. Antipsychotic efficacy was demonstrated in Study ALK3831-A305—There was a statistically significant reduction in the primary efficacy endpoint PANSS score change from baseline at 4 weeks.

The Applicant submitted sufficient information to adequately assess the safety profile of ALKS 3831. In Study ALK3831-A303, there was statistically significant weight mitigation effect compared to olanzapine as demonstrated by the coprimary endpoints percent weight change from baseline and proportion of subjects who gained  $\geq 10\%$  weight from baseline. These results were not supported by favorable metabolic laboratory data trends with ALKS 3831, which may have been related to a limited study duration of 24 weeks; however, there was suggested favorable difference in SBP changes, which is likely beneficial to overall cardiovascular health. Additionally, ALKS 3831 appears to be associated with known atypical antipsychotic class effects, but no new safety signals were seen in the clinical development program. In the context of real-world concurrent opioid use, the potential negative impact of the samidorphan opioid antagonist component could pose a safety risk; the Applicant has addressed this risk in proposed labeling warnings. Review for appropriate mitigation of opioid risk is ongoing at the time of this review completion.

In totality, the direct benefit of ALKS 3831 clinical efficacy appears to outweigh the safety risks of known atypical antipsychotic effects, particularly given the potential mitigation of weight gain, and of potential concurrent opioid use in real-world settings. Therefore, the value of ALKS 3831 is justified as a new treatment option for schizophrenia and bipolar I disorder, and the review team recommends an approval action.

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/s/  
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CATHY A SOUTHAMMAKOSANE  
05/10/2021 08:10:18 AM

BERNARD A FISCHER  
05/10/2021 08:47:17 AM  
Supervisory Physician

## Joint Supervisory Memo

<b>From</b>	Bernard Fischer, MD, Deputy Director and Cross-Discipline Team Leader (CDTL), Division of Psychiatry (DP) Tiffany R. Farchione, MD, Director, DP Eric Bastings, MD, Deputy Director, Office of Neuroscience
<b>Subject</b>	Joint Supervisory Memo
<b>NDA/BLA # and Supplement#</b>	NDA 213378
<b>Applicant</b>	Alkermes, Inc.
<b>Date of Submission</b>	November 15, 2019
<b>PDUFA Goal Date</b>	November 15, 2020 (Action date: November 13, 2020)
<b>Proprietary Name (code name)</b>	Lybalvi (ALKS 3831)
<b>Established or Proper Name</b>	ALKS 3831 combination product
<b>Dosage Form(s) and strengths</b>	Oral tablet
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of schizophrenia in adults [REDACTED] (b) (4) bipolar I disorder in adults
<b>Applicant Proposed Dosing Regimen(s)</b>	Olanzapine 5 mg/Samidorphane 10 mg once daily; Olanzapine 10 mg/Samidorphane 10 mg once daily; Olanzapine 15 mg/Samidorphane 10 mg once daily; Olanzapine 20 mg/Samidorphane 10 mg once daily
<b>Recommendation on Regulatory Action</b>	O-1: Approve O-2: Approve
<b>Recommended Indication(s)/Population(s)</b>	Treatment of schizophrenia in adults; [REDACTED] (b) (4) bipolar I disorder in adults
<b>Recommended Dosing Regimen(s)</b>	Olanzapine 5 mg/Samidorphane 10 mg once daily; Olanzapine 10 mg/Samidorphane 10 mg once daily; Olanzapine 15 mg/Samidorphane 10 mg once daily; Olanzapine 20 mg/Samidorphane 10 mg once daily

# 1. Benefit-Risk Assessment

## Benefit-Risk Assessment Framework

### Benefit-Risk Integrated Assessment

ALKS 3831 is a fixed-dose oral combination product of olanzapine and samidorphan proposed for the treatment of schizophrenia and 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 and indicated for the same indications as those proposed for ALKS3831. 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 combination product contains olanzapine doses of 5, 10, 15, or 20 mg. The samidorphan component is 10 mg for all olanzapine strengths.

Olanzapine is an effective medication for schizophrenia and bipolar I disorder. However, it is associated with substantial weight gain. Medication-induced weight gain has been linked to reduced adherence to treatment, poor self-image, and multiple health problems. The Applicant proposed that the addition of samidorphan to olanzapine would mitigate olanzapine-associated weight gain; thus, decreasing the risk associated with an effective treatment.

The Applicant conducted a relative bioavailability study (A101) comparing ALKS 3831 to an approved form of olanzapine. The results allowed ALKS 3831 to be considered for the same indications as olanzapine—provided the samidorphan component did not interfere with olanzapine’s efficacy. To examine whether samidorphan affects olanzapine’s efficacy, the Applicant conducted Study A305, a 4-week, randomized (1:1:1), double-blind study of ALKS 3831 (olanzapine 10 mg/samidorphan 10 mg) or (20 mg/10 mg), 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. ALKS 3831 was associated with a greater change from baseline on the PANSS than placebo, and the change was both statistically-significant and clinically-meaningful (least-square mean difference of -6.4; 95% CI: -10.2, -2.8). Although no formal noninferiority comparison was proposed, the magnitude of improvement on the PANSS with ALKS 3831 was similar to that observed with olanzapine. Along with the PK bridge to olanzapine (Study A301) and to the prior finding of efficacy of olanzapine for the treatment of schizophrenia and bipolar I disorder, Study A305 supports the efficacy of ALKS 3831 for the treatment of schizophrenia and supports that samidorphan does not meaningfully impair the efficacy of olanzapine as a component of ALKS 3831. Although ALKS 3831 efficacy was not tested in people with bipolar I disorder, there is no reason to believe that the efficacy of olanzapine would be uniquely impaired by samidorphan in people with bipolar I disorder.

To demonstrate the weight-mitigation effect of samidorphan, the Applicant conducted Study A303, 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. Co-primary 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. At end-of-study, the mean change-from-baseline in weight between groups (ALKS 3831 – olanzapine) was -2.38% (95% CI: -3.88%, -0.88%; p=0.002). The proportions of subjects with weight gain of 10% or more from baseline was 17.8% in the ALKS 3831 group and 29.8% in the olanzapine group (p=0.003). Change in waist circumference was a prespecified secondary endpoint in Study A303 and favored ALKS 3831. Although no meaningful differences between ALKS 3831 and olanzapine in lipids or glycemic parameters were observed, it is possible that the 6-month study duration was too short to allow the detection of a benefit of ALKS 3831 on lipids or glycemic parameters. Overall, ALKS 3831 provides a clinically meaningful mitigation of the olanzapine-induced weight gain.

Other than weight gain, the safety profile of ALKS 3831 is generally similar to olanzapine. However, there are risks that samidorphan could precipitate opioid withdrawal in patients who are physically dependent on opioids, lead to ineffective analgesia when medically necessary, or block the high in those with an opioid use disorder. These latter situations could result in overdose if a patient attempts to overcome samidorphan's opioid antagonist effects. These risks can be adequately mitigated through labeling.

Although the Office of Pharmaceutical Quality (OPQ) Review team has assessed NDA 213378 with respect to drug substance, drug product, and biopharmaceutics and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports, there are unresolved quality issues [REDACTED] (b) (4). Therefore, OPQ recommends a Complete Response (CR) action from a product quality perspective.

Overall, the benefit of the mitigation of the weight gain induced by olanzapine clearly outweighs the risks related to the opioid antagonism of samidorphan. A CR letter will be issued because of the CMC deficiencies.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><b>Analysis of Condition</b></p>	<p><u>Schizophrenia</u>            Schizophrenia is a severe and persistent psychotic disorder characterized by disordered perception, thought, and behavior. Symptoms include positive symptoms (such as delusions or hallucinations); disorganized thought, speech, or behavior; negative symptoms (such as diminished emotional expression or avolition); and cognitive impairments (such as impairment in executive function, attention, or memory). Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia—some of this excess mortality is due to increased cardiovascular risk. Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within 1 year after their last episode; most relapses occur in the context of medication. Nonadherence and medication-induced weight gain is one reason for nonadherence. The annual incidence of schizophrenia is approximately 1.5 per 10,000 people, and schizophrenia is one of the leading causes of years lost due to disability worldwide.</p> <p><u>Bipolar I Disorder</u>            Bipolar I disorder is a severe and persistent mental illness</p>	<p>Schizophrenia and bipolar I disorder are serious conditions and are associated with significant disability. Evidence informing the analysis of the condition is from published literature and psychiatric textbooks, as well as clinical experience with this population.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>characterized by episode(s) of mania and, in the majority of cases, episodes of major depression. After one manic episode, greater than 90% of individuals have recurrent mood episodes, and suicide risk is estimated to be at least 15 times the general population risk.</p> <p>Functional impairment is significant: one study found that individuals with bipolar I disorder demonstrate severe impairment in occupational functioning approximately 30% of the time, and individuals with bipolar I disorder attain lower levels of socioeconomic status than members of the general population with equivalent educational levels. As with schizophrenia, one reason for treatment nonadherence is medication-induced weight gain. Aggregate lifetime prevalence estimates for bipolar I disorder range from 0.6 to 1%.</p>	
<p><b>Current Treatment Options</b></p>	<p>Practice guidelines for the treatment of schizophrenia recommend 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. Second-generation, or atypical, antipsychotics (SGAs) are part of various treatment guidelines for bipolar I disorder, and multiple studies have demonstrated their effectiveness.</p> <p>Adverse reactions from antipsychotics vary between drugs, but may include weight gain and metabolic effects,</p>	<p>Antipsychotics reduce the severity of the positive symptoms of schizophrenia and the manic and mixed episodes in bipolar I disorder. Nonadherence to daily oral antipsychotics is common in these conditions and can lead to psychiatric hospitalization and other adverse outcomes. Olanzapine is an effective antipsychotic but is associated with the potential for significant weight gain. Medication-induced weight gain has been cited by patients as one reason for treatment nonadherence.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>extrapyramidal side effects, increased prolactin, sedation, and QT prolongation. Olanzapine is recognized as one of the most effective antipsychotics, but also as having one of the greatest liabilities for medication-induced weight gain.</p>	
<p><b>Benefit</b></p>	<p>The efficacy of ALKS3831 for the proposed indication is established by an adequate PK bridge to listed drug olanzapine (NDA 020592), which allows to rely on a prior finding of efficacy of olanzapine for the proposed indication, and by Study 305, which provides evidence of effectiveness of ALKS 3831 on psychotic symptoms, and supports that the addition of samidorphan to olanzapine does not meaningfully impair the efficacy of olanzapine. Although these studies only enrolled people with schizophrenia, we have no reason to believe the samidorphan component would uniquely interfere with olanzapine’s efficacy for bipolar disorder.</p>	<p>the Applicant has provided substantial evidence of the effectiveness of ALKS 3831 for the treatment of schizophrenia and bipolar disorder in adults through an PK bridge to olanzapine (NDA 020592) and data supporting that the addition of samidorphan to olanzapine does not meaningfully impair the efficacy of olanzapine.</p>
<p><b>Risk and Risk Management</b></p>	<ul style="list-style-type: none"> <li>ALKS 3831 adverse events were largely similar to those of olanzapine. An identified safety issue not already labeled for the LD concerns the risks related to ALKS 3831’s samidorphan component and concurrent opioid use. Specifically, ALKS 3831 can precipitate opioid withdrawal in people with physiological dependence and may block opioid effects (leading to potential overdose if someone tries to overcome samidorphan’s opioid antagonism effects). Labeling can be used to advise prescribers of this potential safety issue and mitigate the</li> </ul>	<p>The Applicant has demonstrated that there is less risk of weight gain with ALKS 3831 than with the LD. Although there is a risk of using ALKS 3831 and opioids concurrently, this risk can be mitigated with labeling.</p> <p>Overall, the improved safety profile of ALKS 3831 versus the LD with regard to weight gain is expected to make a meaningful difference to patients and outweigh potential increases in risk due to concurrent opioid use.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>risk.</p> <ul style="list-style-type: none"><li>• Study A303 demonstrated that, among people who were not currently taking olanzapine, starting ALKS 3831 led to significantly less weight gain than starting olanzapine—both in terms of percent change from baseline and in the proportion of subjects gaining <math>\geq 10\%</math> of their baseline weight.</li><li>• Limited data are available about the effects on pregnancy and lactation. ALKS 3831 is likely to be used by women of child-bearing potential and labeling with reflect this. Any future approval would be accompanied with the postmarketing requirement for a milk-only lactation study.</li></ul>	

## 2. Background

### Product

ALKS 3831 is a fixed-dose oral combination product of olanzapine and samidorphan intended for the treatment of schizophrenia and 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 and indicated for the treatment of schizophrenia and bipolar I disorder. Samidorphan is a new molecular entity (NME) that functions as a mu opioid receptor antagonist with low agonist activity at kappa and delta opioid receptors. The combination product contains olanzapine doses of 5, 10, 15, or 20 mg. The samidorphan component is 10 mg for all olanzapine strengths.

### Regulatory History

ALKS 3831 has not been approved or marketed in any country. In 2012, the Applicant opened Investigational New Drug application 114375 for the prevention of olanzapine-induced weight gain in the Division of Metabolism and Endocrinology Products (DMEP). DMEP and the Division of Psychiatry (DP) agreed that the Investigational New Drug 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- to 8-week study of the effectiveness of ALKS 3831 in the acute treatment of schizophrenia would be necessary to support that the addition of samidorphan did not impair olanzapine's antipsychotic efficacy. 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, designed to assess 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  $\geq 10\%$  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 co-primary endpoints (i.e., superiority on both endpoints required for the study to be deemed positive), which the Applicant incorporated in their 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 that "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."

On May 7, 2019, the Division and Applicant held a pre-NDA meeting. The Applicant submitted the NDA on November 15, 2019; it was filed on January 14, 2020, with a standard review priority. The Agency convened a joint Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee meeting to provide input on whether the degree of weight mitigation was clinically meaningful, and whether the risk related to opioid use and samidorphan could be adequately addressed in labeling (see Section 9).

### 3. Product Quality

The product quality review was performed by:

- Drug substance: Gaetan Ladouceur (primary), Donna Christner (secondary)
- Drug product/Environmental: Mariappan Chelliah (primary), Julia Pinto (secondary)
- Manufacturing: Teng (Daisy) Xu (primary), Yaodong (Tony) Huang (secondary)
- Biopharmaceutics: Assadollah Noory (primary), Ta-Chen Wu (secondary)
- Regulatory Business Process Manager: Teshara Bouie
- Technical lead: Valerie Amspacher

ALKS 3831 is a film-coated, immediate release, fixed-dose combination bilayer tablet (b) (4) (b) (4) Olanzapine USP is an antipsychotic drug approved by the FDA since 1996. Samidorphan is a new molecular entity.

The drug substance information is cross-referenced to DMF (b) (4) which was last reviewed by the Agency on 05/25/2020 (adequate). All the excipients (b) (4) are of compendial grade and their qualities are controlled by their respective compendial testing methods. The Applicant has adequately validated all the non-compendial analytical methods and they are suitable for controlling the quality of the drug product.

The drug product is proposed to be packaged in the following commercial presentations: 7-ct, 30-ct, 90-ct in HDPE bottles with desiccant and fitted with a child-resistant closure. The Applicant has provided up to 18 months of long-term and 6 months of accelerated stability data for the primary batches. In addition, up to 6 months of long-term and accelerated stability data are also available for the supportive batches. (b) (4) (b) (4) The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

The biopharmaceutics review focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) formulation bridging throughout product development between the to-be-marketed drug product to the formulations used in clinical studies, and (3) risk assessment. No deficiency was identified in the biopharmaceutics review.

Pre-approval inspection was required for this NDA because this is the first time this site has manufactured a bilayer tablet. The Office of Pharmaceutical Quality conducted a records review in lieu of an in-person facility inspection. During the review, the Agency identified (b) (4) as a concern. This is a critical defect, and the Applicant had no root-cause analysis (b) (4)

Based on these deficiencies, the Application will receive a Complete Response.

The CMC review team recommends a Complete Response because of the deficiencies identified in manufacturing.

## 4. Pharmacology/Toxicology

The primary pharmacology/toxicology reviewer was Amy Avila; the secondary reviewer was pharmacology supervisor Aisar Atrakchi.

A complete and adequate nonclinical program of studies was conducted for samidorphan, an NME. Nonclinical studies conducted with the combination of ALKS 3831 included pharmacology, pharmacokinetics, a 13-week repeat-dose toxicity study in dogs, and an embryofetal development study in rats.

The nonclinical studies conducted with samidorphan alone, and the combination of olanzapine and samidorphan (ALKS 3831) submitted with the NDA, in addition to the Agency's previous findings of safety of olanzapine, are adequate to support the safety of ALKS 3831 for the proposed indication, at a maximum recommended human dose of ALKS 3831 20 mg/10 mg.

Samidorphan is an antagonist at mu-opioid receptors and a partial agonist at kappa-opioid receptors. Olanzapine is an atypical antipsychotic with activity at serotonin, dopamine, histamine 1, and alpha-adrenergic receptors. In vivo studies in rats co-administered olanzapine and samidorphan demonstrated that samidorphan attenuates olanzapine-induced increases in extracellular dopamine (DA) in response to a high fat diet. More importantly, samidorphan did not alter the activity of olanzapine in a screen for antipsychotic efficacy in rats. Samidorphan was also able to mitigate olanzapine-induced metabolic dysfunction, including weight gain and adiposity, in rats and nonhuman primates; however, it did not prevent olanzapine-induced liver insulin resistance in rats or have any effects on HbA1c levels or glucose tolerance.

In safety pharmacology studies, samidorphan and metabolite RDC-9986 were not significant hERG channel blockers, and samidorphan did not have any significant adverse effects on cardiovascular or respiratory parameters in dogs. Samidorphan exposure in rats had no effects on CNS or neurobehavioral parameters except at the highest dose.

Toxicity of orally administered samidorphan was evaluated in rats and dogs up to 6-months and 9-months in duration, respectively. In rats, the main toxicities observed included a

significant decrease in body weight, which was more pronounced in males than females, and liver histopathology findings (hepatocellular cytoplasmic vacuolation) in high-dose males, which was partially reversible. In dogs, toxicities included a significant decrease in body weight in both sexes, and transient CNS-related clinical signs (e.g., head shaking, excessive salivation) that were reversible after drug cessation.

The effects of the combination of olanzapine and samidorphan was investigated in a 13-week repeat-dose oral toxicity study in dogs, with a 4-week recovery period. No new toxicities were identified with the co-administration of olanzapine and samidorphan, compared to toxicities identified with olanzapine or samidorphan alone. CNS-related clinical signs, including tremors and ataxia, and GI-related signs were observed in males and females after treatment with olanzapine, samidorphan, and the combination. Reversible organ weight changes with accompanying microscopic findings were observed in male and female reproductive tract organs which were attributed to olanzapine.

Samidorphan was evaluated in a complete and adequate battery of genetic toxicology assays, all of which were negative. Samidorphan is also non-carcinogenic.

Samidorphan administration to pregnant rats during the period of organogenesis resulted in decreased fetal weights, increased skeletal variations, and a slight increase in total malformations at doses that were maternally toxic and greater than 248 times the MRHD. Samidorphan administration to pregnant rabbits during the period of organogenesis resulted in no effects on embryofetal development at doses up to approximately 143 times the MRHD. The administration of the combination of samidorphan and olanzapine to pregnant rats during the period of organogenesis resulted in similar effects on embryofetal development as the study with samidorphan administration alone. Samidorphan did not produce any adverse effects on male or female fertility in rats. Samidorphan administration to rats during pregnancy and lactation resulted in reduced pup survival, lower birth weights, and decreased pup body weight gain at doses 188 times the MRHD.

The safety of the major human metabolites, RDC-9986 and RDC-1066, was adequately assessed in nonclinical species for chronic general toxicity, reproductive toxicity, and carcinogenicity. Nonclinical data describing the primary pharmacodynamics, metabolism, genotoxicity, carcinogenicity, and developmental and reproductive toxicity of olanzapine will be taken from the approved label of Zyprexa (NDA 020592), the listed drug for this 505(b)(2) NDA.

The pharmacology/toxicology team recommends approval.

## 5. Clinical Pharmacology

The primary clinical pharmacology review team was Praveen Balimane, Vishnu Sharma, Atul Bhattaram, Yuching Yang, and Manuela Grimstein. The secondary reviewer was team leader Luning (Ada) Zhuang. The final clinical pharmacology signatory was Mehul Mehta.

ALKS 3831 was used for all the key clinical pharmacology studies, such as the single-ascending and multiple-ascending dose studies, organ-impairment studies, food-effect study, and drug-interaction studies. Additionally, several clinical pharmacology studies, including the mass balance study, as well as the abuse-potential studies, were performed with samidorphan alone.

A dedicated study (A101) was conducted to establish a PK bridge to olanzapine as listed drug (LD). The study demonstrated acceptable comparative bioavailability to the LD. A dedicated PK study (33-301) demonstrated that olanzapine does not impact the PK of samidorphan, and samidorphan does not impact the PK of olanzapine. A dedicated food-effect study demonstrated that neither the PK of samidorphan nor of olanzapine is impacted by presence of high-fat and high-protein food.

Study A105 was a dedicated hepatic impairment study that assessed the effect of “moderate” hepatic impairment on the PK of ALKS 3831. Both olanzapine and samidorphan had increases in exposure in subjects with hepatic impairment, as compared with non-impaired subjects. Olanzapine had an approximately 70% exposure increase, whereas samidorphan had an approximately 50% exposure increase. Although subjects with severe hepatic impairment were not included in the study, a physiologically-based PK (PBPK) analysis was performed to estimate the magnitude of increase in samidorphan exposure anticipated in patients with severe hepatic impairment and predicted a 2.6-fold exposure increase in these patients. That increase is similar to the 2.1-fold increase in samidorphan exposure observed in subjects with severe hepatic impairment identified in a dedicated study (b) (4)

Based on available safety data, a 2- to 2.5-fold increase in exposure of samidorphan is not expected to be associated with any additional safety concerns. There are no dose adjustments recommended for the LD in patients with hepatic impairment. Therefore, the clinical pharmacology team agrees that no dose adjustment should be required for ALKS 3831 in patients with hepatic impairment.

Study A106 was a dedicated renal impairment study, which assessed the effect of “severe” renal impairment on the PK of ALKS 3831. Increases in exposure of both olanzapine (50%) and samidorphan (100%) were observed in patients with renal impairment, as compared with patients with normal renal function. Based on available safety data, a 100% increase in the exposure of samidorphan is not expected to be associated with any additional safety concerns. Therefore, no dose adjustments are recommended for patients with mild, moderate, or severe renal impairment. ALKS 3831 is not recommended for patients with end-stage renal disease.

Samidorphan is metabolized via multiple CYP pathways, primarily via CYP3A4 and 3A5, with minor contributions from CYP2C8 and 2C19. No dose adjustment with concomitant use of strong CYP3A inhibitors is needed for olanzapine based on the LD’s label. A PBPK analysis indicated that a strong CYP3A4 inhibitor (e.g., itraconazole) may increase exposure of samidorphan by 60%. However, itraconazole only increased the exposure of samidorphan by 45% in a drug-drug interaction study between buprenorphine/samidorphane and itraconazole. Therefore, no dose adjustments is necessary when ALKS 3831 is used with 3A4 inducers or inhibitors.

ALKS 3831 does not prolong the QT interval to any significant extent at supratherapeutic doses.

The clinical pharmacology team recommends approval, and does not recommend any postmarketing requirements (PMR).

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical Efficacy**

The primary clinical reviewer was Cathy Southammakosane; the secondary reviewer was team leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Eiji Ishida, the secondary reviewer was team leader Peiling Yang, and the final biometrics signatory was James Hung.

The Applicant conducted three studies in support of the efficacy of ALKS 3831 (see Table 1), in addition to the PK study (A101) that established a PK bridge between ALKS3831 and olanzapine, with allows to rely on the prior FDA finding of efficacy of olanzapine for the proposed indication (under NDA 020592). All three studies were adequate and well-controlled with acceptable designs, inclusion and exclusion criteria, and data quality.

**Table 1. Efficacy Studies Conducted by Applicant**

Trial	Design	Daily Dosage	Study Endpoints	Enrolled
ALK3831-A305 (NCT02634346) <sup>a</sup>	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, 20 mg)  or Placebo	<u>Primary:</u> PANSS change from baseline to Week 4  <u>Secondary:</u> CGI-S change from baseline to Week 4	403 adults with schizophrenia
ALK3831-A303 (NCT02694328)	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, 20 mg)	<u>Co-Primary:</u> Percent change in body weight from baseline to Week 24  Proportion of subjects with >10% weight gain from baseline to Week 24	561 adults with schizophrenia
ALK3831-302 (NCT01903837)	Phase 2 Randomized, double-blind, placebo-controlled  <u>Part A:</u> 1-week open-label olanzapine lead-in 12-week double-blind samidorphan addition  <u>Part B:</u> 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  Randomized 1:1:1:1 to added samidorphan 5 mg, 10 mg, 20 mg, or Placebo	<u>Primary:</u> Change in PANSS from randomization to end of Part A (12 weeks)	309 adults with schizophrenia

<sup>a</sup>ClinialTrials.gov identifier.

Source: Reviewer-created.

**Study A305**

Study ALK3831-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. The primary endpoint was the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item scale used to evaluate the presence, absence, and severity of schizophrenia symptoms.

A total of 403 patients were randomized to ALKS 3831 (n=134), olanzapine (N=134), or placebo (n=135). The study arms were fairly well-balanced at baseline. A total of 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/m<sup>2</sup>. The majority of subjects were in normal BMI range (18.5 kg/m<sup>2</sup> to <25 kg/m<sup>2</sup>). 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. Overall, 88% (352/401) of subjects completed the study, and 12% discontinued from the double-blind period.

Treatment with ALKS 3831 was associated with improvement in schizophrenia symptoms. The Applicant’s analysis of the primary efficacy endpoint, confirmed by the Agency, showed the least squares (LS) mean difference (i.e., improvement) from baseline to Week 4 in PANSS was significantly greater with ALKS 3831 relative to placebo (LS mean difference from placebo -6.4 (standard error (SE) 1.8); 95% confidence interval (CI): -10.0, -2.8; p<0.001). LS mean decrease from baseline to Week 4 in PANSS was similar in olanzapine relative to placebo (LS mean difference from placebo -5.3 (SE 1.8); 95% CI: -8.9, -1.7; p=0.004).

**Table 2: Change from Baseline in PANSS Total Score at Week 4 (Study A305)**

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

Source: A305 Clinical Study Report, Table 10, verified by FDA statistical reviewer.

<sup>a</sup> 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

These primary findings were corroborated by the result of the secondary efficacy endpoint CGI-S change from baseline. The LS mean decrease (i.e., improvement) from baseline to Week 4 in CGI-S was significantly greater with ALKS 3831 relative to placebo (LS mean difference from placebo -0.38 (SE 0.12); 95% CI -0.61, -0.14; p=0.002). The LS mean decrease from baseline to Week 4 in CGI-S was similar in olanzapine relative to placebo (LS mean difference from placebo -0.44 (SE 0.12); 95% CI -0.67, -0.2; p<0.001).

Although no formal noninferiority testing was conducted, the improvement in schizophrenia symptoms appeared similar between ALKS 3831 and olanzapine.

### Study 302

Study ALK3831-302 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.

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:  $\leq 0$  kg,  $>0$  kg to  $<1$  kg, or  $\geq 1$  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, the Division felt that this 10-point margin was reasonable in the context of a proof-of-concept study.

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. The study arms were fairly well-balanced on demographic 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.

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, an overall decrease in the PANSS was observed across both treatment groups with a LS mean (SE) change from baseline at Week 12 of -2.9 (0.82) and -2.2 (0.47) for the olanzapine plus placebo and olanzapine plus samidorphan groups, respectively (95% CI: -1.2, 2.5). These changes were similar across all groups, and were supported by stable CGI-S scores (LS mean difference of 0.0; 95% CI: -0.2, 0.1), suggesting a flat dose-response for samidorphan.

Study 302 also explored the effect of samidorphan on weight gain. The Applicant defined two analysis populations:

- 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

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.

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

Body Weight	OLZ +				
	PBO	SAM 5mg	SAM 10mg	SAM 20mg	All SAM
FAS 1, n	74	75	83	67	225
Baseline, mean (SD)	76.0 (12.4)	78.3 (13.9)	77.4 (13.6)	75.8 (12.7)	77.2 (13.4)
% change at week 12, mean (SD) <sup>a</sup>	4.3 (7.1)	2.7 (5.0)	2.1 (5.7)	3.0 (6.0)	2.6 (5.6)
% change at week 12, LS mean (SE)	4.1 (0.5)	2.8 (0.5)	2.1 (0.4)	2.9 (0.5)	2.6 (0.3)
95% CI of LS mean	3.2, 5.0	1.8, 3.7	1.3, 3.0	1.9, 3.8	2.1, 3.1
(OLZ+SAM) – (OLZ+PBO), LS mean (SE)		-1.3 (0.7)	-1.9 (0.6)	-1.2 (0.7)	-1.5 (0.5)
95% CI of LS mean difference		-2.6, 0.0	-3.2, -0.7	-2.5, 0.1	-2.5, -0.4
FAS 2, n	45	50	53	46	149
Baseline, mean (SD)	75.8 (13.3)	79.6 (14.2)	75.6 (12.7)	75.5 (13.1)	76.9 (13.4)
% change at week 12, mean (SD)	5.7 (7.5)	3.8 (4.5)	1.9 (5.7)	1.7 (4.6)	2.4 (5.0)
% change at week 12, LS mean (SE)	5.3 (0.6)	3.8 (0.6)	2.2 (0.6)	1.6 (0.6)	2.6 (0.3)
95% CI of LS mean	4.2, 6.4	2.7, 4.9	1.2, 3.3	0.5, 2.7	1.9, 3.2
(OLZ+SAM) – (OLZ+PBO), LS mean (SE)		-1.4 (0.8)	-3.0 (0.8)	-3.7 (0.8)	-2.7 (0.7)
95% CI of LS mean difference		-3.0, 0.1	-4.6, -1.5	-5.3, -2.1	-4.0, -1.4

Source: Reviewer generated based on 302 Clinical Study Report, Table 17.

<sup>a</sup>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

### Study A303

Study ALK3831-A303 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.

Study 303 and the effect of samidorphan on weight gain are further described below under “Safety”.

Study 303 was not primarily designed to assess the efficacy of ALKS3831 on psychotic symptoms. In Study 3032, there was a similar overall decrease in total PANSS score in both treatment groups, with a LS mean (SE) change from baseline at Week 24 of -8.2 (0.73) and -9.4 (0.72) for the ALKS 3831 and olanzapine groups, respectively. The CGI-S showed similar improvement for ALKS 3831 (LS mean 3.5 (0.6)) and olanzapine (LS mean 3.7 (0.5)).

### Efficacy Conclusion

The efficacy of ALKS3831 for the proposed indication is established by an adequate PK bridge to listed drug olanzapine (NDA 020592), which allows to rely on a prior finding of efficacy of olanzapine for the proposed indication, and by Study 305, which provides evidence of effectiveness of ALKS 3831 on psychotic symptoms, and supports that the addition of samidorphan to olanzapine does not meaningfully impair the efficacy of olanzapine. Although these studies only enrolled people with schizophrenia, we have no reason to believe the samidorphan component would uniquely interfere with olanzapine’s efficacy for bipolar disorder. Therefore, in conjunction with the relative bioavailability data obtained from Study A101, the Applicant has provided substantial evidence of the effectiveness of ALKS 3831 for the treatment of schizophrenia and bipolar disorder in adults.

## 8. Safety

The primary clinical reviewer was Cathy Southammakosane; the secondary reviewer was team leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Eiji Ishida, the secondary reviewer was team leader Peiling Yang, and the final biometrics signatory was James Hung. Division of Diabetes, Lipids, and Obesity consultant reviewer Julie Golden and team lead John Sharretts assisted in evaluation of weight mitigation and metabolic parameters.

In addition to the acute studies described in support of ALKS 3831 antipsychotic efficacy, the Applicant submitted two open-label safety studies (see Table 4).

**Table 4. Long-term Safety Studies**

<b>Trial</b>	<b>Design</b>	<b>Daily Dosage</b>	<b>Study Endpoints</b>	<b>Enrolled</b>
ALK3831-A304 (NCT02873208) <sup>a</sup>	Phase 3 Open-label (ALKS 3831) extension of A303	ALKS 3831 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg	Safety	266 adults with schizophrenia
ALK3831-A306 (NCT02669758)	Phase 3 Open-label (ALKS 3831) extension of A305	ALKS 3831 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg	Safety	281 adults with schizophrenia

<sup>a</sup>ClinialTrials.gov identifier.  
Source: Reviewer-created.

Exposures

Over 1600 subjects have been exposed to at least one dose of ALKS 3831 across various clinical development programs; 663 subjects were exposed for at least 6 months, and 386 exposed for at least 1 year.

Deaths and Serious Adverse Events (SAEs)

Two deaths occurred in people exposed to samidorphan across development programs—but both were unlikely to be related to treatment. In a study that enrolled subjects with schizophrenia and a co-occurring alcohol use disorder, one subject randomized to ALKS 3831 died secondary to chronic obstructive pulmonary disease (COPD). A second subject in that study, who received open-label ALKS 3831 before being randomized to olanzapine treatment, died from alcohol poisoning.

Out of the 951 subjects in Studies A305 and A303, 19 (2%) experienced SAEs. The overall rates of SAEs for ALKS 3831 and olanzapine treatment arms were similar, and there were no notable trends (Table 5).

**Table 5. Serious Adverse Events in Studies A303 and A305.**

	<b>ALKS 3831</b> n (%)	<b>Olanzapine</b> n (%)
<b>Study A303</b>	<b>N=274</b>	<b>N=276</b>
Any Serious TEAE	10 (4)	7 (3)
Drug Abuse	2 (1)	0
Schizophrenia	1 (<1)	3 (1)
Somnolence	1 (<1)	0
Suicidal Ideation	1 (<1)	0
Heart Rate Increased	1 (<1)	0
Infection	1 (<1)	2 (1)
Fracture	1 (<1)	0
Rectal Hemorrhage	1 (<1)	0
Pleural Effusion	1 (<1)	0
Road Traffic Accident	0	1 (<1)
Mental Status Changes	0	1 (<1)
<b>Study A305</b>	<b>N=132</b>	<b>N=132</b>
Catatonia	1 (<1)	0
Death (heroin overdose)	0	1 (<1)

Source: Reviewer-created.

Adverse Events (AEs) Leading to Discontinuation

Out of the 951 subjects in Studies A305 and A303, 71 subjects (7.5%) experienced an AE leading to study discontinuation. The rates and nature of these AEs were similar for the ALKS 3831 and olanzapine treatment arms and were less than in the placebo arm (Study A303: 13% ALKS 3831, 10% olanzapine; Study A305: 1% ALKS 3831, 2% olanzapine). See the clinical review for details on the AEs.

Treatment-emergent AEs

Because Studies A303 and A305 were of different duration, their treatment-emergent AEs are presented separately in Table 6 and Table 7, respectively.

**Table 6. Treatment-emergent AEs in Study A303.**

Preferred Term	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Somnolence	71 (26)	62 (22)
Weight Increased	68 (25)	100 (36)
Dry Mouth	35 (13)	22 (8)
Increased Appetite	32 (12)	35 (13)
Fatigue	20 (7)	11 (4)
Infection	17 (6)	15 (5)
Waist Circumference Increased	17 (6)	22 (8)
Extra Dose Administered	15 (5)	19 (7)
Blood Creatine Phosphokinase Increased	14 (5)	12 (4)
Musculoskeletal Pain	12 (4)	20 (7)
Headache	11 (4)	11 (4)
Liver Function Test Abnormal	11 (4)	11 (4)
Dizziness	9 (3)	12 (4)
Akathisia	9 (3)	4 (1)
Upper Respiratory Tract Infection	8 (3)	20 (7)
Blood Pressure Increased	8 (3)	3 (1)
Neutrophil Count Decreased	7 (3)	6 (2)
Nausea	7 (3)	8 (3)
Constipation	7 (3)	6 (2)
Abdominal Discomfort	6 (2)	3 (1)
Blood Insulin Increased	6 (2)	12 (4)
Weight Decreased	6 (2)	3 (1)
Schizophrenia	5 (2)	8 (3)
Vomiting	5 (2)	6 (2)
Dyslipidemia	5 (2)	11 (4)
Toothache	5 (2)	3 (1)
Blood Prolactin Increased	5 (2)	7 (3)
Dermatitis	5 (2)	4 (1)
Agitation	5 (2)	2 (1)

Source: Reviewer-created.

**Table 7. Treatment-emergent AEs in Study A305.**

Preferred Term	ALKS 3831 N=134 n (%)	Olanzapine N=133 n (%)	Placebo N=134 n (%)
Weight Increased	25 (19)	19 (14)	4 (3)
Somnolence	15 (11)	14 (11)	3 (2)
Dry Mouth	10 (7)	7 (5)	1 (1)
Headache	8 (6)	7 (5)	4 (3)
Anxiety	8 (6)	7 (5)	8 (6)
Upper Respiratory Tract Infection	7 (5)	2 (2)	5 (4)
Agitation	5 (4)	2 (2)	6 (4)
Musculoskeletal Pain	4 (3)	8 (6)	2 (1)
Blood Insulin Increased	4 (3)	2 (2)	1 (1)
Constipation	4 (3)	3 (2)	4 (3)
Toothache	4 (3)	1 (1)	0
Abdominal Discomfort	3 (2)	2 (2)	1 (1)
Dizziness	3 (2)	3 (2)	1 (1)
Neutrophil Count Decreased	3 (2)	1 (1)	0
Liver Function Test Abnormal	3 (2)	5 (4)	0

Source: Reviewer-created.

Open-label Studies A304 and A306 did not reveal any unexpected safety signal in patients treated with ALKS 3831.

#### Laboratory Values and Vital Signs

There were no subjects who met criteria for Hy's law. Liver enzyme increase is a known antipsychotic class effect, and hepatotoxicity has been associated with naltrexone, an opioid antagonist with a mechanism of action similar to that of samidorphan. Subjects in the ALKS 3831 group experienced mean shifts from baseline similar to the olanzapine group, but greater than the placebo group.

Prolactin increase is a known antipsychotic class effect. Subjects in the ALKS 3831 group experienced mean shifts from baseline similar to the olanzapine group, but greater than in the placebo group.

Lipid abnormalities are a known antipsychotic class effect. Subjects in the ALKS 3831 group experienced a greater rate of unfavorable mean shifts from baseline than the olanzapine group across all lipid parameters, particularly for total cholesterol and triglycerides. However, the differences were not clinically meaningful. Both ALKS 3831 and olanzapine group mean shifts were greater than in the placebo group.

Glycemic parameter abnormalities are a known antipsychotic class effect. Subjects in the ALKS 3831 group experienced greater mean shifts from baseline in fasting glucose and insulin, compared to the olanzapine group, in which shifts were similar to these seen in the placebo group.

Leukopenia is a known antipsychotic class effect. Rates of leukopenia and neutropenia were similar between ALKS 3831 and olanzapine.

There were no consistent clinically-meaningful differences in vital signs abnormalities between ALKS 3831 and olanzapine. Orthostatic hypotension is a known antipsychotic drugs class effect. Rates of orthostatic hypotension in Study A303 were higher in the ALKS 3831 group (3.7%) than in the olanzapine group (<1%). However, the listed drug (olanzapine) label reports an orthostatic hypotension rate of 20%. Therefore, the imbalance observed in this study is unlikely clinically significant. ECGs did not reveal any significant ALKS 3831 safety signals.

Extrapyramidal symptoms (EPS) are a known antipsychotic class effect. Overall, rates of EPS in subjects on ALKS 3831 were similar to those observed with approved antipsychotic medications.

A diagnosis of schizophrenia or bipolar disorder is a risk factor for suicidal ideation and behavior (SI/B). Overall, there were no SI/B signals for ALKS 3831 from either AE reporting or from Columbia Suicide Severity Rating Scale monitoring.

#### Weight Mitigation Effect (Study A303)

Study ALK3831-A303 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.

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.

A total of 561 subjects were randomized in Study A303: 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. 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  $\geq 25$  kg/m<sup>2</sup>), with a mean BMI of 25.4 kg/m<sup>2</sup> and a mean weight of 77.2 kg. Demographic and baseline characteristics were well-balanced among groups.

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%).

Based on pre-specified criteria, the Applicant increased the initially targeted samidorphan sample size of 400 (200 per arm) to 540 (270 per arm). To control the overall type I error rate

due to the samidorphan sample size increase, the Cui, Hung, and Wang (CHW) test statistic was pre-specified to derive the p-values from the primary testing of both co-primary endpoints. The mean percent change from baseline in weight (first coprimary endpoint) was significantly lower in patients treated with ALKS 3831 than in patients treated with olanzapine (CHW test;  $p = 0.003$ ). 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 (see Table 8).

**Table 8: Primary Analysis Results for First Coprimary Endpoint (Study A303)**

Treatment Group	Number of Subjects	Mean Baseline Weight (SD), kg	Percent Change From Baseline in Weight	
			LS Mean (SE)	Treatment Difference (ALKS 3831 – Olanzapine) (95% CI)
ALKS 3831	266	77.0 (13.7)	4.2 (0.7)	-2.38
Olanzapine	272	77.5 (13.5)	6.6 (0.67)	(-3.88, -0.88)

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.

The proportion of patients who gained 10% or more weight from baseline to Week 24 (second co-primary endpoint) was significantly lower in subjects treated with ALKS 3831 than in those treated with olanzapine (CHW test;  $p = 0.003$ ). 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 9: Primary Analysis for Second Coprimary Endpoint (Study A303)**

Treatment Group	Number of Subjects	Number <sup>a</sup> (Percent) Subjects With $\geq 10\%$ Increase	Results from Logistic Regression Model	
			Primary Measure Odds Ratio (ALKS 3831/Olanzapine) (95% CI)	Supportive Measure Difference in Relative Risk (ALKS 3831 – Olanzapine) (95% CI)
ALKS 3831	266	47 (17.8)	0.50	-13.7
Olanzapine	272	81 (29.8)	(0.31, 0.80)	(-22.8, -4.6)

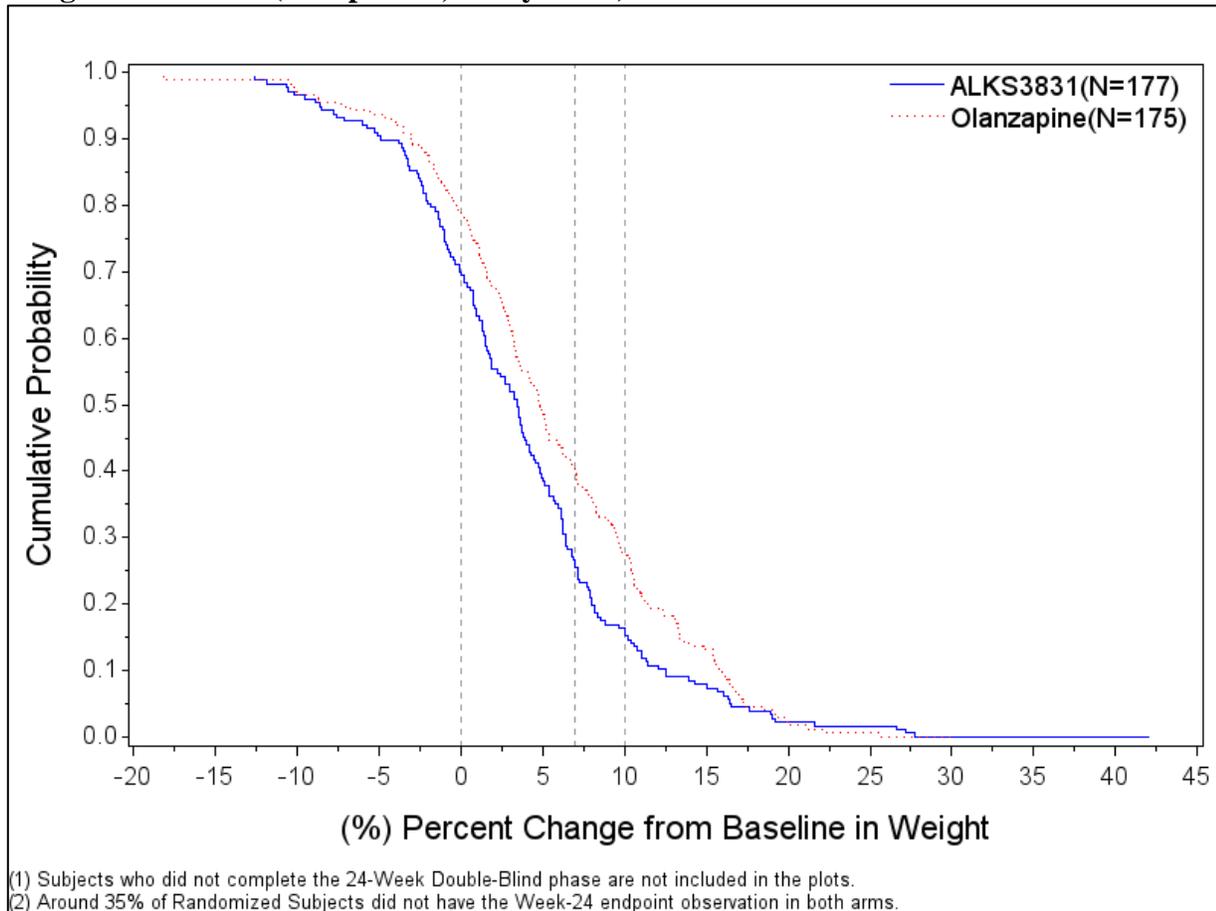
Source: Based on A303 Clinical Study Report, Table 14.2.3, confirmed by FDA statistical reviewer.

<sup>a</sup> 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.

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 1).

**Figure 1. Cumulative Frequency Distribution of Percent Change from Baseline in Body Weight at Week 24 (Completers; Study A303).**



Source: Reviewer-created.

The Division requested long-term follow-up studies to ensure that any weight mitigation observed during Study A303 was not merely a delay of weight gain. That is, that the initial weight mitigation effect continued beyond the acute trials. We did not ask the Applicant to include an olanzapine arm in these studies, so comparisons can only be made via cross-study looks at historical data—which is inherently limited. Nevertheless, we did not see a late excess of weight gain in either of the long-term studies.

The question of whether the observed weight mitigation effect was clinically meaningful in the absence of a favorable difference in metabolic parameters was addressed at an Advisory Committee (AC) meeting (see Section 9). The AC members considered the weight mitigation clinically meaningful. The 6-month duration may have been too short a time period to observe changes in metabolic laboratory values in a population having normal values at baseline.

Study A303 only enrolled people who were not currently taking olanzapine. Therefore, it is unknown whether ALKS 3831 would offer any weight advantage for people already taking olanzapine.

### Opioid-related Safety

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 warrants consideration.

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.

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.

In an ongoing extension of Studies A304 and A306, a subject was hospitalized for an accidental opioid overdose leading to discontinuation of study drug. She initially reported ingesting four tablets of acetaminophen, but drug testing confirmed presence of opioids and the absence of acetaminophen.

The Agency recognizes the potential risks of concurrent opioid and samidorphan use and discussed several potential mitigation strategies (see Division of Risk Management (DRM) Review in Section 11: *Other Relevant Regulatory Issues* and Section 12: *Labeling*). Ultimately, the Agency believes that the risk posed by samidorphan and concurrent opioid use can be mitigated through labeling.

### Determination of Safety

The review team believes the safety of ALKS 3831 is generally similar to olanzapine—although with less risk of weight gain and the potential added risk with concurrent opioid use. The balance of these risks versus benefits for the proposed indications is favorable and risks can be mitigated through labeling.

## 9. Advisory Committee Meeting

The Agency convened a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 9, 2020. Three voting questions and one discussion question were presented to the Committees. The complete discussion is available in the public record via the transcript of the meeting.

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

Result: 16 Yes, 1 No, 0 Abstain

2) VOTE: Has the Applicant adequately characterized the safety profile of ALKS 3831?

Result: 13 Yes, 3 No, 1 Abstain

3) VOTE: Is labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan?

Result: 11 Yes, 6 No, 0 Abstain

4) DISCUSSION: What, if any, additional data are needed to address outstanding issues?

Individual Committee members discussed the following:

- Conducting an efficacy study that would enroll people with bipolar I disorder to confirm that the samidorphan does not interfere with olanzapine's efficacy for this population
- Conducting a long-term weight effect study including an olanzapine comparator arm
- Conducting a study to demonstrate weight mitigation benefit with patients stable on olanzapine, but experiencing ongoing weight gain
- Careful labeling to clearly convey the limitations of the Applicant's demonstrated weight mitigation (i.e., patients on olanzapine who had already experienced weight gain were not studied)
- Conducting a PET occupancy study to better characterize samidorphan and active metabolite opioid receptor pharmacodynamics
- Clearly conveying potential safety risks related to concurrent opioid use

## 10. Pediatrics

The primary pediatrics reviewer from the Division of Pediatric and Maternal Health (DPMH) was Yeruk (Lily) Mulugeta; the secondary reviewer was team leader Shetarra Walker.

The Applicant has an agreed initial pediatric study (iPSP) and, if the drug is approved, several Pediatric Research Equity Act (PREA) postmarketing requirements will be issued (see Section 13: *Postmarketing Recommendations*).

The agreed iPSP includes the following studies:

- A (b) (4) multiple-dose, open-label study to evaluate the safety, tolerability and pharmacokinetics of ALKS 3831 in pediatric subjects (10-12 years old) with bipolar I disorder
- A (b) (4) pediatric study in subjects with schizophrenia or bipolar I disorder to evaluate body mass index and safety of ALKS 3831 compared to olanzapine
- A (b) (4) open-label safety extension study

## 11. Other Relevant Regulatory Issues

### Office of Surveillance and Epidemiology (OSE) Reviews

OSE performed two reviews to offer context for the potential postmarketing safety of the ALKS 3831 samidorphan component:

- A pharmacovigilance memorandum reported on the concurrent use of opioids and a fixed dose combination product containing bupropion and the opioid antagonist naltrexone. The memo was authored by reviewer Alicia Lopez with team leader Vicky Chan and approved by Division of Pharmacovigilance I Director, Cindy Kortepeter. The review found concurrent prescriptions for opioids and the naltrexone-containing product despite contraindications in labeling. However, the review could not assess the risks of this co-prescribing.
- An epidemiology and drug utilization review was completed by reviewers Celeste Mallama and Daniel Bak, with team leaders Rose Radin and Shekhar Mehta, tertiary reviewers Jana McAninch and Rajdeep Gill, and associate office directors Judy Staffa and Grace Chai. The review addressed:
  - The associations between bipolar disorder or schizophrenia and chronic pain/opioid nonmedical use
  - Utilization patterns of olanzapine and opioid-containing products, including concomitant use of these medications

- Epidemiology of opioid overdose or withdrawal associated with use of oral naltrexone, the only orally bioavailable  $\mu$ -opioid antagonist marketed in the United States

The epidemiologic data suggest that chronic opioid use is relatively common among patients with bipolar disorder and that bipolar disorder is associated with both nonmedical opioid use and opioid use disorder. The pattern is less clear in people with schizophrenia, but publications from the 1990s suggest a higher risk of opioid use disorder in people with schizophrenia versus the general population. 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. 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 at least 1 day) opioid prescription claims (either analgesics or cough/cold products).

Based on this data, the Agency believes a prescription for ALKS 3831 and concurrent opioid use would be likely. After discussing several alternatives, the Agency determined that the most appropriate way to mitigate this risk is through labeling (see Section 12: *Labeling*).

#### Division of Risk Management (DRM) Review

DRM, the Office of Neuroscience, and OSE discussed whether a Risk Evaluation and Mitigation Strategy (REMS) would be warranted for ALKS 3831 because of the potential risks related to the samidorphan component and concurrent opioid use. Ultimately, the Agency decided a REMS was not warranted, and noted the precedent for the acceptably safe use of other opioid receptor antagonists (including some combination products) that do not have a REMS.

#### Controlled Substance Staff (CSS) Review

The CSS review was completed by primary reviewer Edward Hawkins (with additional labeling input from Josh Lloyd), and supervisory pharmacologist Chad Reissig.

The CSS review concludes that olanzapine does not have abuse potential and should not be scheduled under the Controlled Substances Act (CSA). Samidorphan is currently controlled in Schedule II of the CSA as a non-specified opiate derivative, but a recommendation to de-schedule was submitted to the Drug Enforcement Agency in December 2019. If ALKS 3831 were approved and samidorphan is still scheduled, the label would include (b) (4)

CSS also participated in labeling discussions on mitigating potential risks related to concurrent opioid use (see Section 12: *Labeling*).

#### Reproduction, Lactation, and Fertility

The primary reviewer for maternal health from DPMH was Catherine Roca; the secondary reviewer was team leader Miriam Dinatale.

No new clinical data were identified on the effects of olanzapine on pregnancy outcomes. Therefore, no changes to current labeling language for the olanzapine portion of LYBALVI are required. Human data on samidorphan and pregnancy or the combination of olanzapine and samidorphan are not sufficient to determine a drug-associated effect on major birth defects, miscarriage or maternal or fetal outcomes. Nonclinical data of the combination of olanzapine and samidorphan showed increase in fetal loss and skeletal abnormalities at 5.5 times the MRHD. A pregnancy registry for antipsychotic medications has been established; this product should be included in this registry.

No new information was identified that will require changes to the olanzapine portion of LYBALVI labeling. Because there are no data on samidorphan and lactation, consideration should be given for a milk-only lactation study given that there is anticipated use of LYBALVI in females of reproductive potential with schizophrenia or bipolar I disorder (see Section 13: *Postmarketing Recommendations*).

Current olanzapine labeling includes subsection 8.3. No new data was located that would change labeling at this time. No clinical data on samidorphan and fertility are available; however, nonclinical data do not indicate an adverse effect on fertility.

#### Division of Medication Error Prevention and Analysis (DMEPA)

The DMEPA review was completed by primary reviewer Loretta Holmes and team leader Sevan Kolejian. The DMEPA review identified no approvability issues.

#### Office of Scientific Investigation Inspections

Per the memo by Jenn Sellers, FDA's Office of Scientific Investigation (OSI), four study sites were inspected:

- Site 840139 (ALK3831-A303), Chicago, Illinois; John S. Sonnenberg, MD
- Site 840246 (ALK3831-A303), Cerritos, California; Morteza Marandi, MD
- Site 840127 (ALK3831-A305), Richardson, Texas; Scott R. Bartley, MD
- Site 840184 (ALK3831-A305), Rogers, Arkansas; Fayz Hudefi, MD

The OSI inspections raised no concerns regarding data quality or integrity; the data generated by these sites appeared acceptable in support of the application.

## **12. Labeling**

This section summarizes the high-level discussions and decisions made for this product's label.

- Potential risk related to concurrent opioid use:
  - The Agency viewed the risks related to concurrent ALKS 3831 and opioid use in two broad categories: risks of starting ALKS 3831 in someone who is physiologically dependent on opioids, and risks of starting opioids in someone on ALKS 3831. The

former situation could precipitate acute opioid withdrawal; the latter may result in inadequate analgesia when medically necessary or an overdose risk if someone tries to overcome the samidorphan opioid receptor blockade. This risk can be addressed in the contraindication section (contraindicating ALKS 3831 in patients using opioids because of the potential to precipitate and acute opioid withdrawal) and the Warnings and Precautions section. (b) (4)

- Warnings and Precautions Section:

- Patients Receiving Opioids: Two sections were added to the label to warn about risks of ALKS 3831 and concurrent opioid use: one about precipitating opioid withdrawal and a second regarding the potential vulnerability to opioid overdose when trying to overcome samidorphan’s opioid receptor blockade or because of changes in opioid tolerance when ALKS 3831 is interrupted.
- (b) (4) This section was removed (b) (4)
- Metabolic Changes: This section was truncated to provide a general statement about glycemic, lipid, and body weight changes; reference is made to Section 14 Clinical Studies where the metabolic data is presented.
- Use in Patients with Concomitant Illness: This section was updated to Anticholinergic (Antimuscarinic) Effects to more precisely describe the issue, to detail risk factors, and to be consistent with the LD PI.

- Adverse Reactions Section:

- (b) (4) were removed for consistency with this section’s objective of presenting ALKS 3831 common AEs (b) (4)
- (b) (4) was removed and replaced by text listing AEs of interest: For subjects in the ALKS 3831 treatment arm, those AEs occurring in >2% of subjects and greater than active-control subjects and, in addition, those with high incidence and were of special interest (e.g., weight increased and increased appetite).

- Use in Specific Populations Section: Language in Pregnancy, Lactation, and Females and Males of Reproductive Potential sections were updated in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).
- Clinical Studies Section:
  - Study ALK3831-A303 was delineated as a Special Safety Study marking its distinction from the antipsychotic efficacy study supporting the indications claims. Weight and metabolic data from ALK3831-A303 were presented in this section, (b) (4).

### 13. Postmarketing Recommendations

The following PMRs would be issued with any future approval:

- Conduct a multiple-dose study to evaluate safety, tolerability, and pharmacokinetics of ALKS 3831 in children 10 to 12 years of age with bipolar I disorder.
- Conduct a (b) (4), double-blind, olanzapine-controlled study enrolling both patients 13 to 17 years with schizophrenia and 10 to 17 years with bipolar I disorder to evaluate change in body mass index and safety of ALKS 3831.
- Conduct a long-term (b) (4) open-label, safety extension study to evaluate the safety and tolerability of ALKS 3831 in pediatric patients.
- Perform a lactation study (milk only) in lactating women who have received therapeutic doses of ALKS 3831, using a validated assay to assess concentrations of olanzapine and concentrations of samidorphan in breast milk and the effects on the breastfed infant.

### 14. Recommended Comments to the Applicant

The Applicant will receive a Complete Response letter due to CMC deficiencies.

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/s/  
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BERNARD A FISCHER  
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ERIC P BASTINGS  
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Clinical/Statistical Review  
 NDA 213378/Original 1  
 NDA 213378/Original 2  
 Lybalvi (Olanzapine/Samidorphan, ALKS 3831)

### NDA/BLA Multi-Disciplinary Review and Evaluation

<b>Application Type</b>	505(b)(2) with New Molecular Entity
<b>Application Number(s)</b>	213378
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	November 15, 2019
<b>Received Date(s)</b>	November 15, 2019
<b>PDUFA Goal Date</b>	November 15, 2020 (Action Date: November 13, 2020)
<b>Division/Office</b>	Division of Psychiatry/Office of Neuroscience
<b>Review Completion Date</b>	November 13, 2020
<b>Established/Proper Name</b>	Olanzapine/Samidorphan
<b>(Proposed) Trade Name</b>	Lybalvi
<b>Pharmacologic Class</b>	Antipsychotic/Opioid receptor antagonist
<b>Code name</b>	ALKS 3831
<b>Applicant</b>	Alkermes, Inc.
<b>Doseage form</b>	Oral Tablet
<b>Applicant proposed Dosing Regimen</b>	Olanzapine 5 mg/Samidorphan 10 mg once daily; Olanzapine 10 mg/Samidorphan 10 mg once daily; Olanzapine 15 mg/Samidorphan 10 mg once daily; Olanzapine 20 mg/Samidorphan 10 mg once daily
<b>Applicant Proposed Indication(s)/Population(s)</b>	Original 1: Treatment of schizophrenia (adults) Original 2: <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> <span style="background-color: #cccccc; display: block; width: 100%; height: 1em; margin-top: 5px;"></span> bipolar I disorder (adults)
<b>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</b>	58214004   Schizophrenia (disorder) 68569003   Manic bipolar I disorder (disorder)
<b>Recommendation on Regulatory Action</b>	Complete Response
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	N/A
<b>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</b>	N/A
<b>Recommended Dosing Regimen</b>	N/A

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<b>Office of Surveillance and Epidemiology (OSE)/ Division of Epidemiology</b>	See separate OSE review
<b>OSE/ Division of Medication Error Prevention and Analysis</b>	Loretta Holmes/Sevan Kolejian
<b>OSE/ Division of Risk Management</b>	Leah Hart

## Glossary

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AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALKS 3831	Applicant code for the olanzapine/samidorphan combination product
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BARS	Barnes akathisia scale
BLA	biologics license application
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression- Improvement
CGI-S	Clinical Global Impression- Severity
CK	creatinine phosphokinase
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
DDLO	Division of Diabetes, Lipid Disorders, and Obesity
DMC	data monitoring committee
DP	Division of Psychiatry
DPMH	Division of Pediatrics and Maternal Health
DSMB	data and safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
EDC	electronic data capture
EOT	end of treatment

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EPS	extrapyramidal symptoms
EQ-5D	EuroQol Quality of Life Scale
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	fasting plasma glucose
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GRMP	good review management practice
HbA1c	hemoglobin A1c
HOMA-IR	homeostasis model assessment-insulin resistance
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IWQOL	impact of weight on quality of life
LD	listed drug
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent to treat
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed effect Model Repeat Measurement
MMTT	mixed meal tolerance test
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OGTT	oral glucose tolerance test
OL	open label
OLZ	olanzapine
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PANSS	Positive and Negative Syndrome Scale
PBRER	Periodic Benefit-Risk Evaluation Report
PCS	potentially clinically significant
PD	pharmacodynamics

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PE	pulmonary embolism
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAM	samidorphan
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SD	standard deviation
SE	standard error
SI/B	suicidal ideation and behavior
SOC	standard of care
SPA	special protocol assessment
TEAE	treatment emergent adverse event
TG	triglycerides

## 1 Executive Summary

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### 1.1 Product Introduction

The Applicant has developed ALKS 3831, a fixed-dose oral combination of olanzapine and samidorphan for:

- The treatment of schizophrenia in adults
- The treatment of bipolar I disorder in adults, including:
  - Treatment of manic and mixed episodes
  - The maintenance of bipolar I disorder
  - As an adjunct to valproate or lithium in the treatment of manic or mixed episodes

Olanzapine is an atypical antipsychotic initially approved in 1996 (as Zyprexa, NDA 020592) for the treatment of schizophrenia in adults; it is currently available in the United States in multiple oral and injectable formulations with indications for schizophrenia, bipolar I disorder (manic and mixed states, maintenance, and adjunctive to lithium or valproate), and, in combination with fluoxetine (as Symbyax, NDA 021520), for acute depressive episodes associated with bipolar I disorder and treatment resistant depression. Samidorphan is a new molecular entity (NME) that functions as a mu opioid receptor antagonist with low agonist activity at kappa and delta opioid receptors. The proposed fixed dosage strengths formulated in bilayer tablets are (olanzapine/samidorphan) 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg<sup>(b) (4)</sup>

## 1.2 Benefit-Risk Assessment

### Benefit-Risk Summary and Assessment

ALKS 3831 is a fixed-dose oral combination product of olanzapine and samidorphan intended for the treatment of schizophrenia and 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 and indicated for the treatment of schizophrenia and bipolar I disorder. 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 combination product contains olanzapine doses of 5, 10, 15, or 20 mg. The samidorphan component is 10 mg for all olanzapine strengths.

Olanzapine is an effective medication for schizophrenia and bipolar I disorder. However, it is associated with substantial weight gain. Medication-induced weight gain has been linked to reduced adherence to treatment, poor self-image, and multiple health problems. The Applicant proposed that the addition of samidorphan to olanzapine would mitigate olanzapine-associated weight gain; thus, decreasing the risk associated with an effective treatment.

The Applicant conducted a relative bioavailability study (A101) comparing ALKS 3831 to an approved form of olanzapine. The results allowed ALKS 3831 to be considered for the same indications as olanzapine—provided the samidorphan component did not interfere with olanzapine's efficacy. To demonstrate noninterference, the Applicant conducted Study A305, a 4-week, randomized (1:1:1), double-blind study of ALKS 3831 (olanzapine 10 mg/samidorphan 10 mg) or (20 mg/10 mg), 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. ALKS 3831 was associated with a greater change from baseline on the PANSS than placebo and the change was both statistically-significant and clinically-meaningful (least-square mean difference of -6.4; 95% CI: -10.2, -2.8). Although no formal noninferiority comparison was proposed, the magnitude of improvement on the PANSS with ALKS 3831 was comparable to that observed with olanzapine. The Agency has reviewed these results and concluded that samidorphan does not impair the efficacy of olanzapine in ALKS 3831. Although ALKS 3831 efficacy was not tested in people with bipolar I disorder, there is no reason to believe that the efficacy of olanzapine would be uniquely impaired by samidorphan in people with bipolar I disorder.

To demonstrate the weight-mitigation effect of samidorphan, the Applicant conducted Study A303, 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. Co-primary 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. At end-of-study, the mean change-from-baseline in weight between groups (ALKS 3831 – olanzapine) was -2.38% (95% CI: -3.88%, -0.88%; p=0.002). The proportions of subjects with weight gain of 10% or more from baseline was 17.8% in the ALKS 3831 group and 29.8% in the olanzapine group (p=0.003). Change in waist circumference was a prespecified secondary endpoint in Study A303 and favored ALKS 3831. Although there were no meaningful differences between ALKS 3831 and olanzapine in lipids or glycemic parameters, it may be that 6 months was too short a time period to detect an ALKS 3831-olanzapine difference.

Other than weight gain, the safety profile of ALKS 3831 is generally similar to olanzapine. However, there are risks that samidorphan could precipitate opioid withdrawal in patients who are physically dependent on opioids or lead to ineffective analgesia when medically necessary/block the high in those with an opioid use disorder. These latter situations could result in overdose if a patient attempts to overcome samidorphan's opioid antagonist effects. After discussing various options to address this risk, the Agency believes these potential opioid-related risks can be mitigated through labeling.

Although the Office of Pharmaceutical Quality (OPQ) Review team has assessed NDA 213378 with respect to drug substance, drug product, and biopharmaceutics and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports, the manufacturing discipline has unresolved quality issues [REDACTED] <sup>(b) (4)</sup>. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until this issue is satisfactorily resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

Based on Agency review of the adequate and well-controlled studies submitted, we have concluded that the benefits of ALKS 3831 outweigh its risks for the treatment of schizophrenia and bipolar I disorder in adults. However, because of the findings related to the manufacturing facility, the application will receive a Complete Response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Analysis of Condition</a></p>	<p><u>Schizophrenia</u></p> <p>Schizophrenia is a severe and persistent psychotic disorder characterized by disordered perception, thought, and behavior. Symptoms include positive symptoms (such as delusions or hallucinations); disorganized thought, speech, or behavior; negative symptoms (such as diminished emotional expression or avolition); and cognitive impairments (such as impairment in executive function, attention, or memory).</p> <p>Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia—some of this excess mortality is due to increased cardiovascular risk.</p> <p>Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within 1 year after their last episode; most relapses occur in the context of medication Nonadherence and medication-induced weight gain is one reason for nonadherence. The annual incidence of schizophrenia is approximately 1.5 per 10,000 people, and schizophrenia is one of the leading causes of years lost due to disability worldwide.</p> <p><u>Bipolar I Disorder</u></p> <p>Bipolar I disorder is a severe and persistent mental illness characterized by episode(s) of mania and, in the majority of cases, episodes of major depression. After one manic episode, greater than 90% of individuals have recurrent</p>	<p>Schizophrenia and bipolar I disorder are serious conditions and are associated with significant disability. Evidence informing the analysis of the condition is from published literature and psychiatric textbooks, as well as clinical experience with this population.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>mood episodes, and suicide risk is estimated to be at least 15 times the general population risk.</p> <p>Functional impairment is significant: one study found that individuals with bipolar I disorder demonstrate severe impairment in occupational functioning approximately 30% of the time, and individuals with bipolar I disorder attain lower levels of socioeconomic status than members of the general population with equivalent educational levels. As with schizophrenia, one reason for treatment nonadherence is medication-induced weight gain.</p> <p>Aggregate lifetime prevalence estimates for bipolar I disorder range from 0.6 to 1%.</p>	
<p><a href="#"><u>Current Treatment Options</u></a></p>	<p>Practice guidelines for the treatment of schizophrenia recommend 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. Second-generation, or atypical, antipsychotics (SGAs) are part of various treatment guidelines for bipolar I disorder, and multiple studies have demonstrated their effectiveness.</p> <p>Adverse reactions from antipsychotics vary between drugs but may include weight gain and metabolic effects, extrapyramidal side effects, increased prolactin, sedation, and QT prolongation. Olanzapine is recognized as one of the most effective antipsychotics, but also as having one of the greatest liabilities for medication-induced weight gain.</p>	<p>Antipsychotics reduce the severity of the positive symptoms of schizophrenia and the manic and mixed episodes in bipolar I disorder. Nonadherence to daily oral antipsychotics is common in these conditions and can lead to psychiatric hospitalization and other adverse outcomes. Olanzapine is an effective antipsychotic but is associated with the potential for significant weight gain. Medication-induced weight gain has been cited by patients as one reason for treatment nonadherence.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Benefit</a></p>	<p>Study A101 demonstrated acceptable comparative bioavailability between ALKS 3831 and the listed drug (LD). Therefore, the Agency could rely on the efficacy findings for the LD in the treatment of schizophrenia and bipolar I disorder provided that the samidorphan component did not interfere with olanzapine’s efficacy.</p> <ul style="list-style-type: none"> <li>• Study A305, supported by findings from Studies A303 and 302, demonstrated that ALKS 3831 led to a statistically-significant and clinically-meaningful reduction in the symptoms of schizophrenia. This reduction was comparable to that observed with olanzapine alone.</li> </ul>	<p>The Applicant provided evidence that meets the evidentiary standard to support marketing approval.</p> <p>Study A101 demonstrated comparative bioavailability and Study A305 (supported by data from Studies A303 and 302) demonstrated that the samidorphan component did not interfere with olanzapine’s efficacy. Although ALKS 3831 efficacy was not tested in people with bipolar I disorder, there is no reason to believe that the efficacy of olanzapine would be uniquely impaired by samidorphan in people with bipolar I disorder.</p>
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>• ALKS 3831 adverse events were largely similar to those of olanzapine. An identified safety issue not already labeled for the LD concerns the risks related to ALKS 3831’s samidorphan component and concurrent opioid use. Specifically, ALKS 3831 can precipitate opioid withdrawal in people with physiological dependence and may block opioid effects (leading to potential overdose if someone tries to overcome samidorphan’s opioid antagonism effects). Labeling can be used to advise prescribers of this potential safety issue and mitigate the risk.</li> <li>• Study A303 demonstrated that, among people who were not currently taking olanzapine, starting ALKS 3831 led to significantly less weight gain than starting olanzapine—both in terms of percent</li> </ul>	<p>The Applicant has demonstrated that there is less risk of weight gain with ALKS 3831 than with the LD. Although there is a risk of using ALKS 3831 and opioids concurrently, this risk can be mitigated with labeling.</p> <p>Overall, the improved safety profile of ALKS 3831 versus the LD with regard to weight gain is expected to make a meaningful difference to patients and outweigh potential increases in risk due to concurrent opioid use.</p>

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	<p>change from baseline and in the proportion of subjects gaining <math>\geq 10\%</math> of their baseline weight.</p> <ul style="list-style-type: none"><li>Limited data are available about the effects on pregnancy and lactation. ALKS 3831 is likely to be used by women of child-bearing potential and labeling with reflect this. Any future approval would be accompanied with the postmarketing requirement for a milk-only lactation study.</li></ul>	

### 1.3 Patient Experience Data

#### Patient Experience Data Relevant to this Application

X	<b>The patient experience data that were submitted as part of the application include:</b>	Section of review where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO)	ALK3831-A303 and ALK3831-A307 Section 5.3.5.1 ALK3831-A304, ALK3831-A306, and ALK3831-A308 Section 5.3.5.2
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	X Clinician reported outcome (ClinRO)	ALK3831-A303, ALK3831-A305, and ALK3831-A307 Section 5.3.5.1 ALK3831-A304, ALK3831-A306, and ALK3831-A308 Section 5.3.5.2
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify):	
	<input type="checkbox"/> <b>Patient experience data that were not submitted in the application, but were considered in this review:</b> <input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	

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<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data was not submitted as part of this application.</b>	

## 2 Therapeutic Context

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### 2.1 Analysis of Condition

#### Schizophrenia

Schizophrenia is a severe and chronic mental illness affecting approximately 1% of the population.<sup>1</sup> Onset of illness is typically between late adolescence and the third decade of life.<sup>2</sup> This persistent, disabling disease is characterized by disordered perception, thought, and behavior, with deficits in social and occupational functioning. Symptoms include disorganized thought, speech, or behavior and cognitive impairment along with positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal and lack of emotion, energy, and motivation) symptoms. Diagnosis is made clinically, based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria (see Table 1). Individuals who develop schizophrenia vary substantially in terms of onset, symptom presentation, and outcome.

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<sup>1</sup> Association, A.P., *Diagnostic and statistical manual of mental disorders (DSM-5)*. 2013: American Psych Pub.

<sup>2</sup> Tandon, R., H.A. Nasrallah, and M.S. Keshavan, *Schizophrenia. Clinical features and conceptualization*. Schizophrenia Research, 2009. 110(1):p.1-23.

**Table 1. Diagnostic Criteria for Schizophrenia**

<p>A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):</p> <ol style="list-style-type: none"><li>1. Delusions</li><li>2. Hallucinations</li><li>3. Disorganized speech (e.g., frequent derailment or incoherence)</li><li>4. Grossly disorganized or catatonic behavior</li><li>5. Negative symptoms (i.e., diminished emotional expression or avolition)</li></ol> <p>B. For a significant period of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).</p> <p>C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).</p> <p>D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.</p> <p>E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.</p> <p>F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).</p>
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Source: *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*

### **Bipolar I Disorder**

Bipolar I disorder is a severe and persistent mental illness affecting approximately 1% of the population.<sup>3</sup> The mean age at onset for the first mood episode is approximately 18 years. This disease is characterized by episodic mania and, in the majority of cases, episodes of major depression. The diagnostic manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. Diagnosis is made clinically based on the DSM-5 criteria (see Table 2). The course of bipolar I disorder is quite variable in terms of types of episodes, frequency and duration of episodes, and residual interepisode symptomatology.

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<sup>3</sup> Merikangas, K.R., et al., *Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication*. Arch Gen Psych, 2007. 64(5):543-52.

**Table 2: Diagnostic Criteria for Manic Episode**

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
  - 1. Inflated self-esteem or grandiosity
  - 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
  - 3. More talkative than usual or pressure to keep talking
  - 4. Flight of ideas or subjective experience that thoughts are racing
  - 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
  - 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless, non-goal-directed activity)
  - 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or to another medical condition.

Source: *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*

## 2.2 Analysis of Current Treatment Options

### Schizophrenia

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.<sup>4</sup> The mechanism by which antipsychotics improve psychotic symptoms is not completely understood but may involve antagonism of dopamine D2 receptors and/or 5-HT<sub>2A</sub> receptors. Binding to other neurotransmitter receptors (e.g.,  $\alpha$ 1-adrenergic, muscarinic, and histaminergic receptors) generally corresponds to the adverse reaction profile for a given drug.<sup>5</sup> A number of antipsychotics are currently available for the treatment of schizophrenia (see Table 3).

Some of the relevant class-based safety issues for antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic

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<sup>4</sup> Lehman, A.F., et al., *Practice guidelines for the treatment of patients with schizophrenia*. American Journal of Psychiatry, 2004. 161(2 SUPPL).

<sup>5</sup> Correll, C.U., *Mechanism of action of antipsychotic medications*. J Clin Psychiatry, 2014. 75(9): p.e23.

hypotension, weight gain, metabolic changes, seizures, blood dyscrasias, and an increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis. In general, the typical antipsychotics have been associated with more extrapyramidal side effects compared to the atypical antipsychotics, although the latter are not devoid of this adverse effect. The atypical antipsychotics have been associated with more weight gain, hyperglycemia, and hyperlipidemia side effects compared to the typical antipsychotics. Within each class of typical or atypical antipsychotic, the incidence of these adverse effects varies.

Although there are a number of approved treatments for schizophrenia, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably-tolerated treatment is identified. Additionally, most available medications predominantly affect positive symptoms but do not appear to meaningfully impact negative symptoms or cognitive impairment.

### Bipolar I Disorder

In terms of pharmacological treatment for bipolar I disorder, the mood stabilizer mainstays of lithium and the antiepileptic valproate have been joined by multiple SGAs and the mood stabilizer antiepileptics lamotrigine and carbamazepine extended-release capsules.<sup>6</sup> As with schizophrenia, although there are a number of approved treatments for bipolar I disorder, individual patient response cannot be predicted. For an individual patient, several trials of different products may be required before an effective and tolerable treatment can be identified.

**Table 3: Summary of Available Pharmacologic Treatments**

Product (s) Name	Relevant Indication
Aripiprazole	Schizophrenia Bipolar disorder: manic and mixed episodes and maintenance
Asenapine	Schizophrenia Bipolar disorder: manic and mixed episodes and maintenance
Brexpiprazole	Schizophrenia
Carbamazepine	Bipolar disorder: manic and mixed episodes
Cariprazine	Schizophrenia Bipolar disorder: manic, mixed, and depressive episodes
Chlorpromazine	Schizophrenia
Clozapine	Schizophrenia
Fluphenazine	Psychotic disorders
Haloperidol	Schizophrenia
Iloperidone	Schizophrenia

<sup>6</sup> Hirschfeld, R.M., *Guideline watch: Practice guideline for the treatment of patients with bipolar disorder, 2<sup>nd</sup> edition*. 2011: American Psych Pub.

Product (s) Name	Relevant Indication
Lamotrigine	Bipolar disorder: maintenance
Lithium	Bipolar disorder: maintenance
Loxapine	Schizophrenia
Lurasidone	Schizophrenia Bipolar disorder: depressive episode
Molindone	Schizophrenia
Olanzapine	Schizophrenia Bipolar disorder: manic and mixed episodes and maintenance
Olanzapine/fluoxetine	Bipolar disorder: depressive episode
Paliperidone	Schizophrenia and schizoaffective disorder
Perphenazine	Schizophrenia
Prochlorperazine	Schizophrenia
Quetiapine	Schizophrenia Bipolar disorder: manic, mixed, and depressive episodes and maintenance
Risperidone	Schizophrenia Bipolar disorder: manic and mixed episodes and maintenance
Thioridazine	Schizophrenia
Thiothixene	Schizophrenia
Trifluoperazine	Schizophrenia
Ziprasidone	Schizophrenia Bipolar disorder: manic and mixed episodes and maintenance
Valproate	Bipolar disorder: manic episode

Source: Reviewer-generated.

### Metabolic Considerations

Adverse metabolic effects, including hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain, are well-described sequelae of olanzapine and other atypical antipsychotics that contribute to lack of compliance with treatment and cardiometabolic disease burden in this vulnerable patient population.

Olanzapine in particular has been associated with these adverse effects. 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 (a potential marker of antipsychotic efficacy); however, significantly more patients on olanzapine discontinued drug due to adverse events, primarily due to weight gain and metabolic effects (9% vs. 1% to 4% for the other drugs).<sup>7</sup>

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<sup>7</sup> Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209-23.

Weight gain and metabolic effects are listed in the Warnings and Precautions section of the olanzapine prescribing information (PI). Weight gain from clinical trials in adults is described in Table 4.

**Table 4: Olanzapine Weight Gain in Clinical Trials as Described in Labeling**

	OLZ	Placebo
<b>13 placebo-controlled olanzapine monotherapy studies</b>		
Mean weight change, median 6 weeks	+2.6 kg	-0.3 kg
Proportion 7% weight gain, median 8 weeks	22.2%	3.0%
Proportion 15% weight gain, median 12 weeks	4.2%	0.3%
Weight gain discontinuation	0.2%	0%
<b>Long-term studies, at least 48 weeks, median 573 days, N=2,021</b>		
Mean weight change	+5.6 kg	
Proportion 7% weight gain	64%	
Proportion 15% weight gain	32%	
Proportion 25% weight gain	12%	
Weight gain discontinuation	0.4%	

Source: Zyprexa PI

The Applicant reports that certain patients appear to be at greater risk from olanzapine-induced weight gain, such as those with early weight gain, those with a lower body mass index (BMI), those with less prior exposure to antipsychotics, and younger patients.<sup>8</sup>

Weight gain with olanzapine has been described as rapid during the first few weeks, slowing gradually, and plateauing after several months.<sup>9</sup> Weight gain in the first few weeks of olanzapine treatment is associated with longer-term weight gain.<sup>10,11</sup> For example, in one paper, patients who experienced early weight gain were more than three times as likely to experience long-term weight gain as those who did not. Among 669 patients analyzed, approximately 39% of patients who gained 2 kg or more at Week 3 experienced a weight gain of 10 kg or more by Week 30, while approximately 12% of patients who gained less than 2 kg by Week 3 experienced a weight gain of 10 kg or more by Week 30.<sup>10</sup>

<sup>8</sup> NDA 213378, Integrated Summary of Efficacy (ISE)

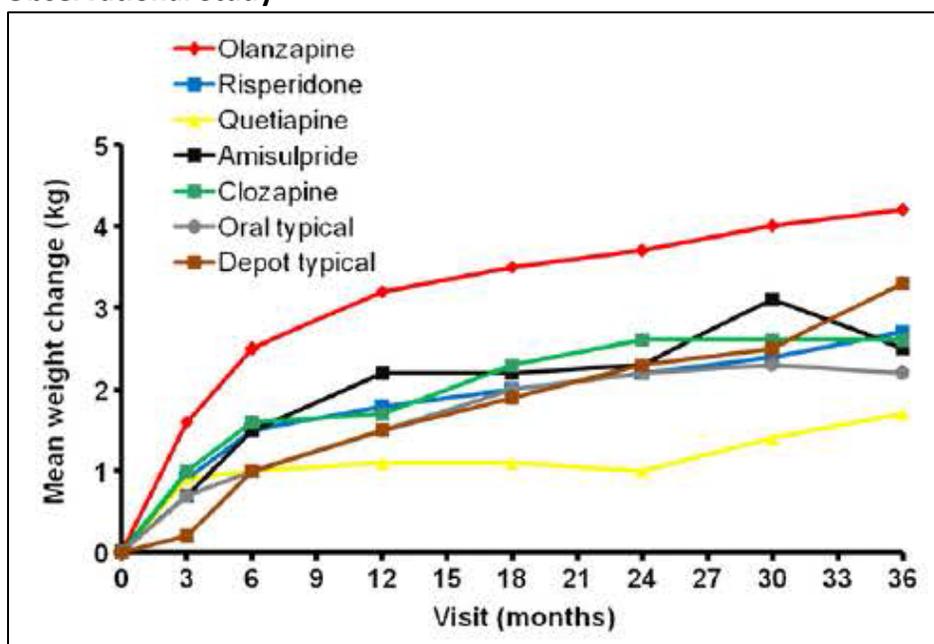
<sup>9</sup> Hasnain M, et al. Weight gain and glucose dysregulation with second-generation antipsychotics and antidepressants: a review for primary care physicians. *Postgrad Med.* 2012;124(4):154-67.

<sup>10</sup> Lipkovich I, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol.* 2006;26(3):316-20.

<sup>11</sup> Lipkovich I, et al. Early evaluation of patient risk for substantial weight gain during olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder. *BMC Psychiatry.* 2008;8:78-92.

A 3-year prospective, nonrandomized observational study<sup>12</sup> 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<sup>13</sup> for the outpatient treatment of schizophrenia (European SOHO). This particular post hoc 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). Most of the weight gain was observed in the first 3 to 6 months for all treatments (Figure 2).

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

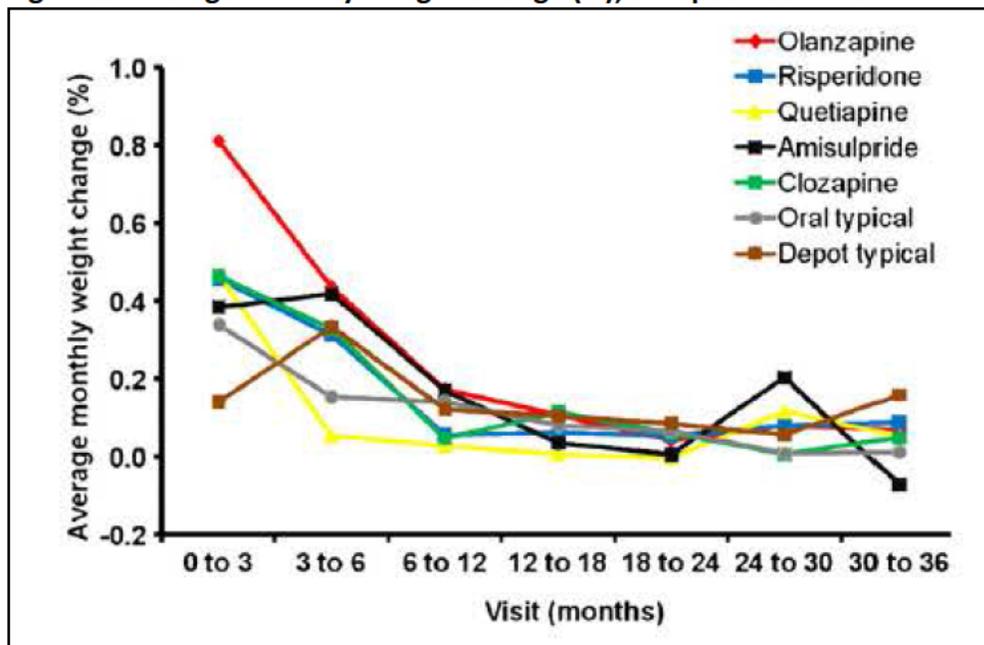


Source: Reference 12, Figure 1; quetiapine-treated patients had a higher BMI at baseline

<sup>12</sup> Novick D, et al. Tolerability of outpatient antipsychotic treatment: 36-month results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Eur Neuropsychopharmacol.* 2009;19(8):542-50.

<sup>13</sup> Olanzapine, risperidone, quetiapine, amisulpride, clozapine, oral typical, and depot typical antipsychotics

Figure 2: Average Monthly Weight Change (%), European SOHO Observational Study



Source: Reference 12, Figure 2; quetiapine-treated patients had a higher BMI at baseline

In this study, a trend was seen for an inverse relationship between baseline BMI and weight gain with olanzapine:

Table 5: Change in Weight from Baseline to 36 Months by Baseline BMI, Olanzapine Group, European SOHO Observational Study

Baseline BMI (kg/m <sup>2</sup> )	n	Mean Weight Change (kg ± SD)
< 20 Underweight	155	8.4 ± 8.6
20-25 Normal weight	1114	5.6 ± 7.9
25-30 Overweight	1007	3.2 ± 8.2
> 30 Obese	365	0.7 ± 10.9

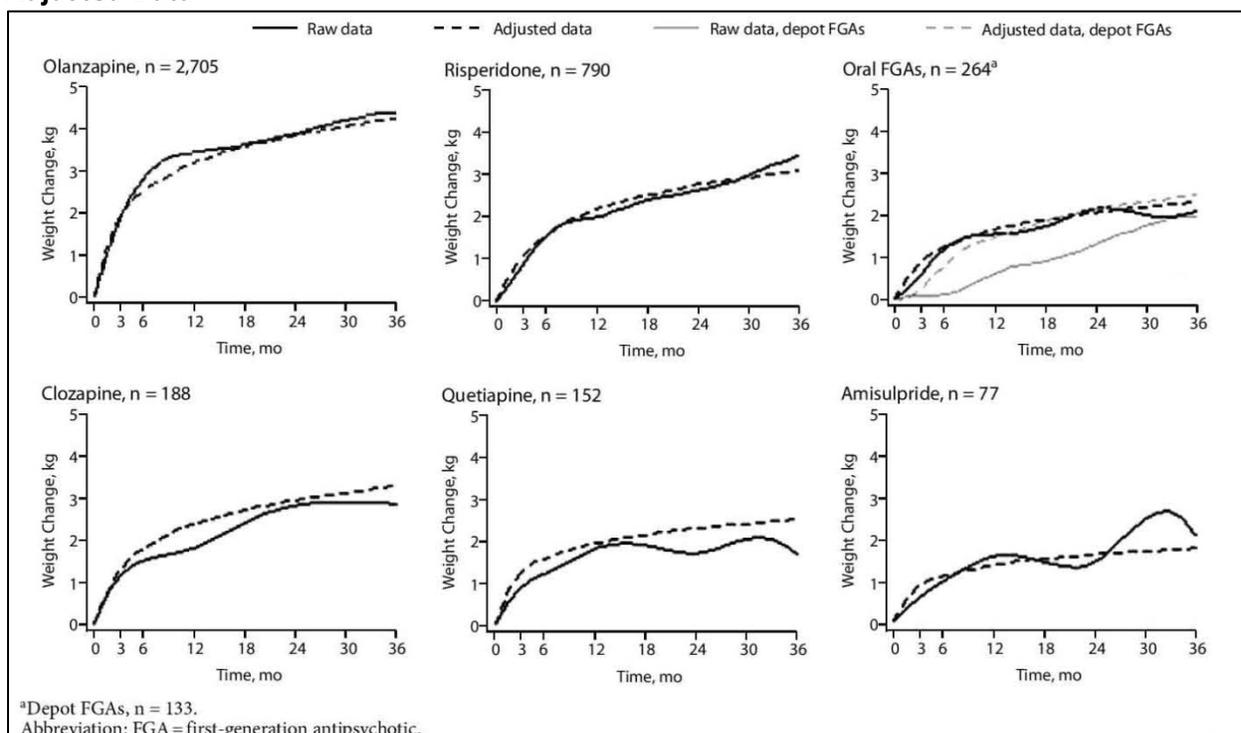
Source: Reference 12, Table 5

Another publication reported the evaluation of additional post-hoc SOHO observational data ('Worldwide SOHO').<sup>14</sup> Weight change was evaluated in 4,626 patients completing 3 years of

<sup>14</sup> Bushe CJ, et al. Weight change from 3-tyear observational data: findings from the worldwide schizophrenia outpatient health outcomes database. J Clin Psychiatry. 2012;73(6):e749-55.

antipsychotic monotherapy with amisulpride, clozapine, olanzapine, quetiapine, risperidone, and oral and depot first-generation antipsychotics. The results were consistent with the European SOHO discussed above, with highest weight gain observed with olanzapine (4.2 kg, 95% CI 3.9, 4.5). As Figure 3 shows, weight change for all antipsychotics was most rapid during the first 6 months; subsequent weight change was slower but did not plateau.

**Figure 3: Trajectory of Mean Weight Change from Baseline (kg) over 3 Years: Raw and Adjusted Data**



Adjusted analyses account for baseline weight, time, age, CGI score, treatment, sex, region, independent house status, involvement in social activities, antipsychotic use before study entry, and time-by-treatment group and weight at study entry-by-treatment group interaction terms

Source: Reference 14, Figure 4

While weight gain and metabolic effects such as type 2 diabetes and dyslipidemia are well-described with olanzapine, the underlying pathophysiology has been debated. Some studies have suggested that metabolic changes occur independent of weight gain, while others have demonstrated an association. Furthermore, studies have shown discordant results regarding the roles of caloric intake and energy expenditure in weight gain.

Two short-term metabolic trials (9 to 28 days) evaluating olanzapine in healthy subjects

illustrate the controversies. In one study<sup>15</sup>—which used a euglycemic-hyperinsulinemic clamp to assess insulin sensitivity and a mixed-meal test to assess postprandial hyperglycemia after 9 days of olanzapine, aripiprazole, or placebo—olanzapine was associated with postprandial hyperglycemia, and both olanzapine and aripiprazole decreased insulin sensitivity. The authors postulated that atypical antipsychotics, and in particular, olanzapine, directly impact early metabolic changes *independent* of weight or fat gain. However, a 28-day metabolic study<sup>16</sup> found substantial rapid weight gain with olanzapine, mild weight gain with iloperidone, and no weight gain with placebo. Gains in body weight and fat mass in olanzapine-treated subjects were associated with increased caloric intake but not changes in energy expenditure in this study. This study showed trends in insulin resistance (by oral glucose tolerance test) and dyslipidemia *in the setting of* acute weight gain.

In summary, weight gain is associated with almost all of the atypical antipsychotics, but olanzapine-associated weight gain appears to be the most egregious. The mechanism behind this weight gain is unclear—as is the relationship between the weight gain and observed metabolic disturbances.

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<sup>15</sup> Teff KL, et al. Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. *Diabetes*. 2013;62(9):3232-40.

<sup>16</sup> Ballon JS, et al. Pathophysiology of drug induced weight and metabolic effects: findings from an RCT in healthy volunteers treated with olanzapine, iloperidone, or placebo. *J Psychopharmacol*. 2018;32(5):533-40.

### 3 Regulatory Background

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#### 3.1 U.S. Regulatory Actions and Marketing History

Olanzapine and samidorphan in combination is not currently marketed in the United States for any indication.

#### 3.2 Summary of Presubmission/Submission Regulatory Activity

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 Division of Psychiatry (DP) agreed that the IND should reside in DP, and it was transferred in 2013.

On December 12, 2013, FDA met with the Applicant to discuss the development pathway and appropriate clinical outcomes for a new indication: [REDACTED] (b) (4)

[REDACTED] The Division did not agree the proposed population [REDACTED] (b) (4)

On May 8, 2015, the Applicant submitted a request [REDACTED] (b) (4)

[REDACTED] he Division denied the request for the following reasons:

[REDACTED] (b) (4)

On June 10, 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- 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 and placebo with an olanzapine arm to demonstrate assay sensitivity. The primary outcome variable needed to measure schizophrenia symptoms (e.g., PANSS). 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.

FDA agreed to the Initial Pediatric Study Plan (iPSP) for ALKS 3831 for schizophrenia. This iPSP was subsequently amended to include both schizophrenia and bipolar I disorder indications for which olanzapine is approved as a second-line agent in the pediatric age group 13 years and older. Subsequently, the pediatric age range to be studied was modified to include subjects ages 10 to 13 years, which is standard for bipolar disorder, and the Agency agreed to this amended PSP.

On September 25, 2015, the Applicant submitted a special protocol assessment (SPA) for Study A303 assessing weight gain of 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  $\geq 10\%$  weight gain at Week 24 was a secondary endpoint. The Division sent a SPA-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 co-primary endpoints. The Division also voiced concern for the potential number of study drop-outs over 24 weeks and how missing data would be handled. Importantly, the Division communicated to the Applicant that approval would rest upon demonstrating ALKS 3831 provided antipsychotic efficacy with significantly less weight gain than olanzapine as evidenced by all of the following:

- Antipsychotic efficacy compared to placebo in Study A305
- Mean differences in percent weight change from baseline in Study A303
- Categorical differences in weight change (i.e., proportion of subjects with  $\geq 7\%$  or  $\geq 10\%$  weight gain) in Study A303
- Effects on laboratory based metabolic parameters in Study A303

The Division 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.” A revised SPA was not submitted.

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On October 24, 2017 in a Type C Written Response, the Division agreed with the Applicant's utilization of a PK bridging strategy, clinical evidence of similar ALKS 3831 antipsychotic effectiveness to olanzapine, and a drug interaction study demonstrating no clinically significant effect with coadministration of lithium and valproate to support the filing for the bipolar I disorder indication.

The Applicant submitted the proposed proprietary name of Lybalvi on November 16, 2018, and the Division of Medication Error Prevention and Analysis conveyed the conditional acceptance of the name on May 8, 2019.

On May 7, 2019, the Division and Applicant held a pre-NDA meeting. The Applicant clarified that they are seeking indications for the treatment of schizophrenia and bipolar I disorder and not seeking an indication for weight mitigation. The Division noted that a description of weight mitigation data in labeling would be a de facto claim and voiced concern that weight differences between ALKS 3831 and olanzapine were modest and the clinical significance was difficult to interpret. The Applicant disagreed and pointed to a difference in weight trajectory by treatment group for those who withdrew from the study (i.e., those who withdrew from the study showed greater weight gain than those who continued on ALKS 3831).

The Applicant submitted the NDA on November 15, 2019; it was filed on January 14, 2020, with a standard review priority.

## **4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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### **4.1 Office of Scientific Investigations (OSI)**

OSI clinical investigators completed inspections: There were some minor unreported adverse events (AE) at two sites, but several of these AEs are already included in the olanzapine label. Otherwise, study conduct was deemed adequate and inspected clinical data at the respective sites appeared reliable. Please refer to the OSI review for detailed discussion.

### **4.2 Product Quality**

A facility deficiency was found [REDACTED] (b) (4)

[REDACTED] Based on this deficiency, the Office of Pharmaceutical Quality (OPQ) is recommending a Complete Response action. Please refer to the OPQ review for a more detailed discussion.

### **4.3 Clinical Microbiology**

Not applicable.

### **4.4 Devices and Companion Diagnostic Issues**

Not applicable.

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## **5 Nonclinical Pharmacology/Toxicology**

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See separate Nonclinical Review (primary author Amy Avila).

## **6 Clinical Pharmacology**

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See separate Clinical Pharmacology Review (primary author Praveen Balimane).

## **7 Sources of Clinical Data and Review Strategy**

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### **7.1 Table of Clinical Studies**

The clinical development program for ALKS 3831 comprised 18 clinical studies: ten phase 1 studies, two phase 2 studies, and six phase 3 studies. Additionally, the development program included nine clinical studies evaluating samidorphan alone: seven phase 1 studies and two phase 2 studies. There was one negative phase 2 study for adults with schizophrenia and alcohol use disorder. The efficacy and safety studies submitted for this NDA are one phase 2, proof-of-concept study (Study 302) and the following phase 3 studies: Study A303 evaluating weight mitigation, Study A305 assessing antipsychotic efficacy, and Studies A304 and A306 which are long-term, safety-extension studies. Another phase 3, long-term, safety-extension study (A308) and one phase 3, randomized, double-blind, active-controlled study of young adults with schizophrenia, schizophreniform disorder, or bipolar I disorder are ongoing. In this review, we refer to the studies by their three- or four-digit suffix (e.g., ALK3831-XXXX).

**Table 6: Listing of Major Clinical Trials for ALKS 3831**

Trial	NCT no.	Design	Daily Dosage	Study Endpoints	Subjects Enrolled	Study Population	Numbers of Centers and Countries
<b>Controlled Studies to Support Efficacy and Safety</b>							
ALK383 1-302	01903837	Phase 2 Randomized, double-blind, placebo-controlled  <u>Part A:</u> 1-week open-label olanzapine lead-in 12-week double-blind samidorphan addition  <u>Part B:</u> 12-week active-treatment olanzapine and samidorphan 4-week open-label olanzapine follow-up	Olanzapine 5, 10, 15, 20 mg based on individual titration  Randomized 1:1:1:1 to added samidorphan 5mg 10mg 20mg or Placebo	Primary: Change in PANSS from randomization to end of Part A (12 weeks)  Exploratory: Percent change in body weight from randomization to end of Part A (12 weeks)	309	Schizophrenia	United States 42 Bulgaria 9 Czech Republic 1
ALK383 1-A303	02694328	Phase 3 Randomized, double-blind, olanzapine-controlled Weight mitigation study  24 Weeks	Randomized 1:1 to ALKS 3831 (10mg/10mg, 20mg/10mg)  or Olanzapine (10, 20 mg)	Co-Primary: Percent change in body weight from baseline to Week 24  Proportion of subjects with $\geq 10\%$ weight gain from baseline to Week 24	561	Schizophrenia	United States 64

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Trial	NCT no.	Design	Daily Dosage	Study Endpoints	Subjects Enrolled	Study Population	Numbers of Centers and Countries
ALK383 1-A305	02634346	Phase 3 Randomized, double-blind, olanzapine- and placebo-controlled Antipsychotic efficacy study  4 Weeks	Randomized 1:1:1 to ALKS 3831 (10mg/10mg, 20mg/10mg)  or Olanzapine (10, 20 mg)  or Placebo	Primary: PANSS change from baseline to Week 4	403	Acute exacerbation of schizophrenia	United States 17 Bulgaria 10 Serbia 9 Ukraine 8
<b>Studies to Support Safety</b>							
ALK383 1-A304	02694328	Phase 3 Open-label (ALKS 3831) extension of A303  52 weeks	ALKS 3831 10mg/10mg 15mg/10mg 20mg/10mg	Safety	266	Schizophrenia	United States 45
ALK383 1-A306	02634346	Phase 3 Open-label (ALKS 3831) extension of A305  52 weeks	ALKS 3831 10mg/10mg 15mg/10mg 20mg/10mg	Safety	281	Schizophrenia	United States 14 Bulgaria 9 Serbia 6 Ukraine 8

Source: Clinical Reviewer.

## 7.2 Review Strategy

This review of ALKS 3831 for both efficacy and safety with regard to the proposed indications of the treatment of schizophrenia and bipolar I disorder in adults was conducted by the statistical reviewer Eiji Ishida, the DDLO clinical reviewer Julie Golden and secondary reviewer John Sharretts, and DP clinical reviewer Cathy Southammakosane.

For the efficacy review, we focused on the pivotal phase 3 trial for acute exacerbation of schizophrenia (A305) along with brief analyses of the supportive phase 2 proof-of-concept trial (302) and the pivotal phase 3 trial assessing weight gain in subjects with schizophrenia (A303; antipsychotic efficacy was not a primary endpoint). We present analyses performed by the Applicant and by our statistical reviewer, Eiji Ishida. The clinical pharmacology team provides supplemental information regarding PK comparative bioavailability models for efficacy, dosing, and adverse events of interest in their own review.

The safety review includes a focus on ALKS 3831's weight mitigation effect based on the results from Study A303 in addition to a general safety review (using the same pivotal trials and proof-of-concept trial mentioned above along with analyses of two long-term open-label safety extension trials, Studies A304 and A306). The 120-Day Safety Update was also reviewed. AE and investigational analyses were conducted with JMP 14 and JMP Clinical 7.1 with the support of the Core Data Fitness Assessment program sponsored by Center for Drug Evaluation and Research's Office of Computational Sciences (OCS).

## 8 Clinical and Statistical Evaluation

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### 8.1 Review of Relevant Individual Trials Used to Support Efficacy and Safety

#### 8.1.1 ALK3831-A305

“A Phase 3 Study to Determine the Antipsychotic Efficacy and Safety of ALKS 3831 in Adult Subjects with Acute Exacerbation of Schizophrenia”

##### 8.1.1.1 Overview and Objectives (Study A305)

###### *Primary Objective*

To evaluate the antipsychotic efficacy of ALKS 3831 compared to olanzapine and placebo in adults with an acute exacerbation of schizophrenia over 4 weeks.

###### *Secondary Objective*

To evaluate the safety and tolerability of ALKS 3831 in adults with an acute exacerbation of schizophrenia.

##### 8.1.1.2 Trial Design (Study A305)

This study was a randomized, double-blind, multinational, multicenter, parallel-group, placebo-controlled inpatient design comparing two doses of ALKS 3831 (10/10 mg daily and 20/10 mg daily) to olanzapine (10 mg daily and 20 mg daily) and placebo over a 4-week treatment period. The subjects were ages 18 to 70 years who were diagnosed with schizophrenia and experiencing an acute exacerbation.

###### *Key inclusion criteria*

- Schizophrenia diagnosed via DSM-5 criteria on psychiatric evaluation and confirmed using Mini International Neuropsychiatric Interview (MINI)
- A PANSS score of  $\geq 80$  with a score  $\geq 4$  on at least three of the following PANSS Positive Scale items: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution
- A CGI-S score of  $\geq 4$

###### *Key exclusion criteria included*

- Psychiatric hospitalization for more than 30 days during the 90 days before screening
- Onset of active-phase schizophrenia symptoms or initiation of first antipsychotic treatment within the 12 months prior to screening

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- Diagnoses of schizoaffective disorder; bipolar I or II disorder; current untreated or unstable major depressive disorder; cognitive difficulties including dementia, delirium, or amnestic syndromes, or any other cognitive disorder present within the past 2 years; drug-induced or toxic psychosis; or any other psychiatric condition that could have interfered with participation in the study
- Suicide risk in the opinion of the Investigator or as confirmed by Items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS)
- PANSS score improved  $\geq 30\%$  from Visits 1 to 2
- History of treatment resistance defined as failure to respond to two adequate trials of different antipsychotic medications
- History of clozapine use within 6 months prior to screening or any history of clozapine use for treatment-resistance schizophrenia
- History of poor or inadequate response to olanzapine treatment
- Olanzapine, mesoridazine, chlorpromazine, or thioridazine treatment during the 6 months prior to screening
- Long-acting injectable antipsychotic medication in the 6 months prior to screening with the exception of paliperidone which must not have been received within 12 months prior to screening
- Moderate or severe alcohol or drug use disorder at screening or during the 3 months prior to screening
- Positive urine drug screen for opioids, amphetamine/methamphetamine, phencyclidine, or cocaine
- Opioid agonist use within the 14 days prior to screening
- Anticipated opioid medication need during the study period
- Opioid antagonist use within 60 days prior to screening
- Use of weight loss or hypoglycemic agents

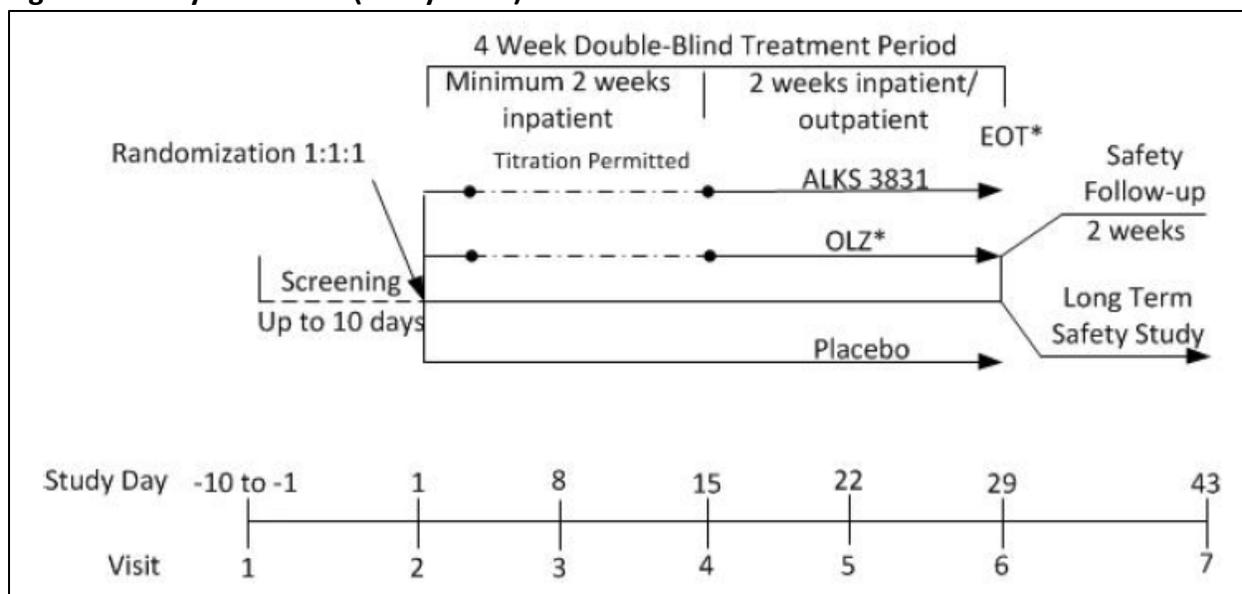
- Use of statin medication initiated or dose-adjusted within the 3 months prior to screening
- Clinically significant or unstable medical illness, condition, or disorder or abnormal screening laboratory assessment or ECG

*Randomization and Blinding*

Subjects were randomized in a 1:1:1 ratio to one of three treatment arms (placebo, ALKS 3831 10/10 mg titrated to 20/10 mg, and olanzapine 10 mg titrated to 20 mg). Randomization occurred centrally via an Interactive Response Technology. Placebo, ALKS 3831, and olanzapine treatments were matching coated bilayer tablets. During the inpatient period, subjects were administered study drug; following discharge, subjects were given study drugs to take home. Study and clinical staff, subjects, and caregivers were blinded to treatment assignment until database lock.

*Study Schematic*

**Figure 4: Study Schematic (Study A305)**



Source: Applicant’s Clinical Study Report for ALK3831-A305, Figure 1, page 19

*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 10/10 mg or olanzapine 10 mg daily from Days 1 to 2 then 20/10 mg or 20 mg, respectively, daily thereafter. If the titrated dose was not tolerated, the dose was allowed to be decreased to 10/10 mg or 10 mg, respectively, at the end of Weeks 1 or 2; no other dose changes were permitted during the study. The doses were selected based on approved lowest and highest olanzapine doses and study data from Study ALK3831-302.

*Study Schedule*

On the day of screening, subjects were admitted to the inpatient study facility for 2 weeks; subjects were discharged at Weeks 2, 3, or 4, if meeting discharge criteria. Subjects who were discharged at Weeks 2 or 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. The assessment schedule was as follows:

**Table 7: Schedule of Assessments (Study A305)**

Period	Screening	Double-Blind Treatment Period					Follow-Up <sup>1</sup>
Visit Number	1	2	3	4	5	6	7
Study Day	-10 to -1	1	8	15	22 <sup>2</sup>	29/ET <sup>2</sup>	43 <sup>2</sup>
Informed Consent	X						
Demographics	X						
Medical/ Psychiatric History	X						
Mini International Neuropsychiatric Interview (MINI)	X						
Eligibility Criteria Review	X	X <sup>3</sup>					
Genotype Sample	X						
Height	X						
Weight and waist circumference (conducted 3 times each visit)	X	X <sup>3</sup>				X	X
Physical Examination <sup>4</sup>	X	X <sup>3</sup>				X	X
Randomization		X					
Urine Drug Screen <sup>5</sup>	X	X <sup>3</sup>			X <sup>6</sup>	X <sup>6</sup>	
Pregnancy Testing	X	X <sup>3</sup>					
Serology Testing <sup>7</sup>	X						
Laboratory Samples <sup>8</sup> (refer to Table 2 of the protocol)	X	X <sup>3</sup>		X		X	
PK Sample <sup>9</sup>		X <sup>3</sup>		X		X	
Vital Signs <sup>10</sup>	X	X <sup>3</sup>	X	X	X	X	X
12-Lead Electrocardiogram	X	X <sup>3</sup>	X	X	X	X	X

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Adverse Event Monitoring	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>11</sup>	X	X <sup>3</sup>	X	X	X	X	X
Abnormal Movement Scales <sup>12</sup>		X <sup>3</sup>	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS) <sup>13</sup>	X	X <sup>3</sup>	X	X	X	X	
Modified Overt Aggression Scale <sup>14</sup>		X	X	X	X <sup>15</sup>	X <sup>15</sup>	
Clinical Global Impression – Severity (CGI-S)	X <sup>16</sup>	X	X	X	X	X	
Clinical Global Impression – Improvement (CGI-I)			X	X	X	X	
Informed Consent for ALK3831-A306						X <sup>17</sup>	
Emergency treatment card <sup>18</sup>		X				X	
Admission to Inpatient Unit <sup>19</sup>	X						
Discharge from Inpatient Unit <sup>20</sup>				X	X	X	
Study Drug Dispensation <sup>21</sup>		X	X	X	X		
Study Drug Return and Adherence Review			X	X	X	X	

Source: Applicant’s Clinical Study Report for ALK3831-A305, Figure 3, page 31

*Study Discontinuation*

Subjects could be removed from the study for an AE, and any therapeutic measures were at the discretion of the Investigator. Any ongoing AEs were to be followed until resolution, deemed stable by the Investigator, or the subject was lost to follow-up.

*Prohibited Medications*

The following medications were not permitted during the study:

- Any other psychotropic medications with the exception of at least 30-day stable dose of:
  - Antidepressants
  - Benzodiazepines to treat sleep symptoms
  - Beta blockers, antihistamines, and anticholinergics to treat extrapyramidal symptoms
- Varenicline, although nicotine replacement patch and gum were permitted
- Any prescription or over-the-counter weight reduction medication
- Systemic steroids
- Topiramate
- Calcitonin
- Medications contraindicated with olanzapine or exhibited drug-interaction potential
- Moderate to strong cytochrome P450 3A4 inducers or inhibitors
- Opioid agonists within 14 days before screening
- Opioid antagonists within 60 days before screening

*Treatment Compliance*

Study personnel monitored treatment adherence with scheduled drug accountability records

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for the amount of study drug dispensed versus the amount returned with check-in between assessments to monitor adherence.

#### *Data Quality Assurance*

The protocol, Investigator's Brochure, electronic case report form instructions, and AE reporting procedure were reviewed with the Investigator or designee at each site, and trainings were conducted at each site initiation visit and during region specific Investigator Meetings. Data was recorded onto appropriate source documents according to GCP procedures and entered into the electronic data capture (EDC) system, which maintained a full audit trail. An Alkermes monitor or designee reviewed source records on site and compared them to eCRF data. Laboratory results and ECGs were transferred electronically from the central laboratories to the EDC database. AEs were coded using MedDRA 19.0; concomitant medications were categorized using the World Health Organization Anatomical Therapeutic Chemical drug dictionary Enhanced with Herbal version.

An investigation was launched secondary to potential unblinding of data to study personnel via the clinical database; two project personnel, but no clinical site or Alkermes Clinical Operations personnel, were exposed to the unblinded data, and on adjudication, it was determined there was no impact to the study data integrity. Additionally, a study center was audited for report of potential data falsification; upon adjudication, it was determined there was no data falsification or general misconduct at the site.

#### **8.1.1.3 Study Endpoints (Study A305)**

##### *Primary Endpoint*

- Change from baseline in PANSS total score at Week 4

##### *Secondary Endpoint*

- Change from baseline in Clinical Global Impression of Severity Scale (CGI-S) at Week 4

##### *Other Endpoints*

- PANSS total score and subscale scores change from baseline by visit
- CGI-S score change from baseline by visit
- Clinical Global Impressions—Improvement (CGI-I) by post-Baseline visit

#### **8.1.1.4 Statistical Analysis Plan (Study A305)**

##### *Sample size considerations*

The planned sample size was 390 subjects in total, 130 subjects per treatment group (ALKS3831, olanzapine, placebo). This was expected to provide 90% power to demonstrate the superiority of ALK 3831 to placebo, assuming a 10-point improvement of PANSS total score at

Week 4, a standard deviation (SD) of 20, and a dropout rate of 30%. Olanzapine served as an active control, hence was not considered in sample size calculation.

### *Analysis Populations*

#### Safety Population

The Safety population included subjects who were randomized and received at least one dose of study drug during the double-blind treatment period.

#### Full Analysis Set (FAS)

The FAS was defined as all subjects who were randomized, received at least one dose of study drug, and had baseline and at least one post-baseline efficacy measure in PANSS score. The FAS was used for efficacy analysis.

### *Primary Analysis*

The primary analysis for both the primary and the secondary endpoint was based on a mixed model with repeated measurements (MMRM) with an unstructured variance-covariance matrix. The model included region (U.S. vs. non-U.S.), visit, treatment, and interaction term of visit and treatment as categorical variables, and baseline PANSS total score as a covariate. All observed measures on the primary analysis set will be included. Missing data will not be imputed.

### *Multiplicity Adjustment*

Since olanzapine served as an active control, multiplicity adjustment for type I error control does not apply to the olanzapine group. The planned sample size is 390 subjects in total, and 130 subjects per treatment group. This sample size will provide at least 90% power to show superiority of the ALKS 3831 group compared to the placebo group at a 2-sided alpha level of 0.05, assuming a 10-point improvement of PANSS total score at Week 4, a standard deviation (SD) of 20, and a dropout rate of 30%.

### *Sensitivity Analysis for Missing Data*

To assess the robustness of the primary analysis with respect to missing data, the Applicant pre-specified a sensitivity analysis using a Delta-adjusted Pattern Mixture Model. It incorporates the clinical assumption that ALKS 3831 subjects who discontinue at a given time point would have, on average, their unobserved PANSS worsened by some amount  $\delta$  compared with the observed PANSS of subjects on the same treatment arm who continue to the next timepoint. Subjects who discontinue from the placebo arm would have the same PANSS trajectory as the placebo subjects who stay on the study. A sequential regression-based multiple imputation (MI) procedure will be used to incorporate the assumption and to allow uncertainty in the imputations to be reflected appropriately in the analysis. The imputation model will include the measurement at the current timepoint as the response variable, and region (U.S. vs. non-U.S.) as factor, the measurements at the previous timepoints and the baseline as covariates. Twenty imputations will be carried out. For each of the 20 imputed data sets, the ANCOVA model with

region (U.S. vs. non-U.S.) and treatment group as factors and baseline PANSS as covariate will be fitted to the change from baseline at Week 4 to obtain the treatment effect estimate and standard error. Rubin's rule will be used to combine the treatment effect estimates and standard errors across imputations. The shift parameters to be used in the sensitivity analysis will account for 10%, 20%, 30%, 40%, and 50% of the observed treatment difference between ALKS 3831 and placebo.

#### **8.1.1.5 Protocol Amendments (Study A305)**

One protocol amendment occurred after the original protocol was finalized on August 5, 2015. The amendment was finalized on September 22, 2016: The key secondary endpoint was changed from MOAS change from baseline to CGI-S change from baseline. There was no change to the SAP.

#### **8.1.1.6 Results (Study A305)**

##### *Compliance with Good Clinical Practices*

The Applicant conducted this study in accordance with Good Clinical Practices principles, the International Conference on Harmonization Guidelines E6, and local regulations. Audits were conducted at six sites. All protocols and amendments were reviewed by each clinical site's Institutional Review Board. An attestation was included in Section 5 of the CSR.

##### *Financial Disclosure*

The study was conducted at 64 sites total in the United States. Eight principal investigators and two subinvestigators reported financial disclosures, consisting of a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria and significant equity interest. See Appendix 17.2 for more details. Study design minimizes potential bias because it was a randomized, blinded trial with objective endpoints.

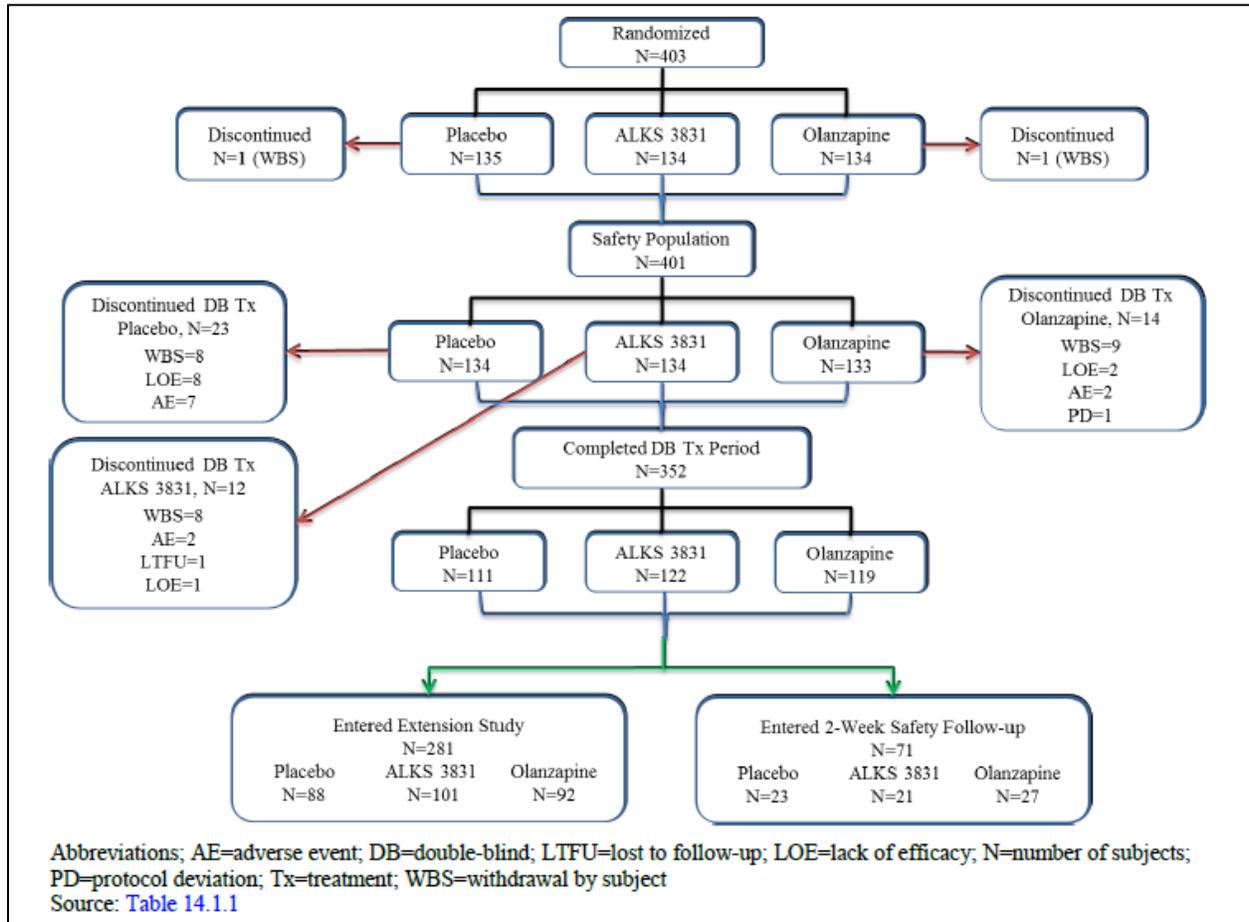
##### *Data Quality and Integrity*

Datasets appeared to be of good quality and were complete. The reviewers have no concerns about data integrity.

##### *Patient Disposition*

Four hundred and three subjects were randomized in this study: 135 to placebo, 134 to ALKS 3831 treatment, and 134 to olanzapine treatment. There were 352 subjects who completed the study (82.8% of the placebo group, 91.0% of the ALKS 3831 group, and 89.5% of the olanzapine group). The active treatment arms were evenly distributed with similar rates of discontinuation in the ALKS 3831 (9.0%) and olanzapine (10.5%) treatment arms, which were less than placebo rates of discontinuation (17.2%). Discontinuations because of AEs were lower in the active drug arms (1.5% of subjects in each active drug arm) than with placebo (5.2%).

**Figure 5: Patient Disposition (Study A305)**



Source: Clinical Study Report for ALK3831-A305, Figure 2, page 44

**Table 8: Subject Population by Treatment (Study A305)**

Category	Treatment Groups			All Subjects
	Placebo	ALKS 3831	Olanzapine	
Subjects Randomized, N	135	134	134	403
Subjects Randomized but not dosed, N	1	0	1	2
Reasons for Discontinuation, n				
Withdrawal by Subject	1	0	1	2
Subjects in Safety Population <sup>a</sup> , N	134	134	133	401
Subjects in Full Analysis Population (FAS) <sup>b</sup> , N	133	132	132	397
Subjects Who Completed Double-blind Treatment Period, n (%)	111 (82.8)	122 (91.0)	119 (89.5)	352 (87.8)
Subjects Who Discontinued Double-blind Treatment Period, n (%)	23 (17.2)	12 (9.0)	14 (10.5)	49 (12.2)
Reasons for Treatment Discontinuation, n (%)				
Adverse Event	7 (5.2)	2 (1.5)	2 (1.5)	11 (2.7)
Lost to Follow-up	0	1 (0.7)	0	1 (0.2)
Lack of Efficacy	8 (6.0)	1 (0.7)	2 (1.5)	11 (2.7)
Protocol Deviation	0	0	1 (0.8)	1 (0.2)
Withdrawal by Subject	8 (6.0)	8 (6.0)	9 (6.8)	25 (6.2)
Subject Continuing into the Long-term Safety Extension Study, n (%)	88 (65.7)	101 (75.4)	92 (69.2)	281 (70.1)

Abbreviations: FAS=Full Analysis Set; N=number of subjects

Note: Percentages are based on the number of subjects in the Safety Population.

a The Safety Population includes all randomized subjects who received at least 1 dose of study drug during the double-blind treatment period.

b The Full Analysis Set (FAS) includes all subjects in the Safety Population who have at least one postbaseline PANSS assessment.

Source: Table 14.1.1

Source: Clinical Study Report for ALK3831-A305, Table 4, page 43

### *Protocol Violations/Deviations*

The Applicant identified six subjects as having major protocol deviations: five in the placebo group and one in the olanzapine group. Four of the six deviations were receiving prohibited medication. All six subjects remained in the FAS population. Additionally, two subjects, one each in the placebo and olanzapine groups, did not meet full inclusion criteria, and one subject in the placebo group inadvertently received a single dose of ALKS 3831 20/10 mg without any associated AEs. These incidents, collectively, were low in number and unlikely to affect the overall efficacy results.

*Demographic Characteristics*

In overall enrollment, there was a higher percentage of white males and subjects who were overweight; slight male preponderance is typical for a population with schizophrenia. Although this was an international study, sites outside of the United States were located in Europe, and minority representation was inadequate and lower than their rates in the general United States population. Therefore, this study's findings may be of limited generalizability to those groups. There were slight demographic imbalances between treatment arms for sex, race, and region: more men were randomized to the ALKS 3831 group, whites to the olanzapine group, and subjects in the United States to the ALKS 3831 group. These demographic imbalances were small and, therefore, unlikely clinically significant. Additionally, subjects randomized to the olanzapine group had higher mean baseline weight and BMI and a greater proportion were obese (BMI  $\geq 30$  kg/m<sup>2</sup>) compared to the other two treatment groups. This weight discrepancy may impact weight mitigation efficacy analysis, although weight was not a prespecified endpoint in this study.

**Table 9: Demographic Characteristics of the Primary Efficacy Analysis (Study A305)**

	ALKS 3831 (N=132)	Olanzapine (N=132)	Placebo (N=133)	Total (N=397)
<b>Sex, n (%)</b>				
Male	83 (63)	80 (61)	78 (59)	241 (61)
Female	49 (37)	52 (39)	55 (41)	156 (39)
<b>Age</b>				
Mean years (SD)	40.8 (12.5)	41.6 (10.9)	41.3 (10.5)	41.2 (11.3)
Median (years)	40	42	40	41
Min, max (years)	18, 65	19, 67	20, 65	18, 67
<b>Race, n (%)</b>				
White	86 (65)	98 (74)	90 (68)	274 (69)
Black/African American	41 (31)	33 (25)	38 (29)	112 (28)
Asian	1 (1)	0	3 (2)	4 (1)
American Indian/Alaska Native	0	0	1 (1)	1 (<1)
Native Hawaiian/other Pacific Islander	1 (1)	0	0	1 (<1)
Other	3 (2)	1 (1)	1 (1)	5 (1)
<b>Ethnicity, n (%)</b>				
Hispanic/Latino	2 (2)	7 (5)	4 (3)	13 (3)
Not Hispanic/Latino	130 (99)	125 (95)	129 (97)	384 (97)
<b>Region, n (%)</b>				
United States	51 (41)	50 (38)	49 (37)	153 (39)
Rest of the World	78 (59)	82 (62)	84 (63)	244 (62)
<b>Weight</b>				
Mean kg (SD)	77.9 (15.5)	81.9 (19.1)	76.8 (15.9)	78.9 (17.0)
Median (kg)	78.0	78.6	75.9	77.3
Min, max (kg)	44.0, 128.2	50.0, 141.4	44.4, 113.9	44.0, 141.4

	ALKS 3831 (N=132)	Olanzapine (N=132)	Placebo (N=133)	Total (N=397)
<b>Body Mass Index</b>				
Mean kg/m <sup>2</sup> (SD)	26.4 (4.5)	27.4 (5.4)	25.9 (4.8)	26.6 (4.9)
Median (kg/m <sup>2</sup> )	25.8	26.3	25.0	25.7
Min, max (kg/m <sup>2</sup> )	19.2, 39.1	18.7, 39.2	17.6, 38.5	17.6, 39.2

Source: Clinical Study Report for ALK3831-A305 Table 14.1.3.2

#### *Other Baseline Characteristics*

Rates of baseline medical and psychiatric morbidity were similar between treatment groups as were baseline PANSS and CGI-S scores.

**Table 10: Baseline PANSS and CGI-S Scores (Study A305)**

	ALKS 3831 (N=132)	Olanzapine (N=132)	Placebo (N=133)
Mean PANSS (SD)	101.8 (11.6)	100.6 (12.1)	102.7 (11.9)
Median PANSS	102.0	99.0	102.0
Min, Max PANSS	80, 144	80, 137	80, 147
Mean CGI-S (SD)	5.1 (0.7)	5.1 (0.7)	5.1 (0.7)
Median CGI-S	5.0	5.0	5.0
Min, Max CGI-S	4.0, 7.0	4.0, 7.0	4.0, 7.0

Source: Clinical Study Report for ALK3831-A305 Table 10, page 52 and Table 12, page 59

#### *Treatment Compliance, Concomitant Medications, and Rescue Medication Use*

Treatment compliance was high and similar between treatment groups ( $\geq 99.8\%$  with no subjects  $< 90\%$  compliant). As noted in the protocol description, olanzapine dose was titrated from 10 mg to 20 mg after 3 days; olanzapine could be titrated down to 10 mg at the end of Weeks 1 or 2 if there were tolerability issues, at the discretion of the Investigator. No further dose adjustments were allowed beyond Week 2. Overall, mean dose of olanzapine was similar between both active treatment groups: 18.4 mg. Similar numbers of subjects had a prior history of psychotropic medication use across treatment groups ( $> 95\%$ ); the most commonly used were antipsychotics and benzodiazepines. There was also similarity in concomitant medication use between all groups; the most commonly used were benzodiazepines and ibuprofen. More subjects in the placebo group received prohibited medications—two subjects received another antipsychotic; this is not expected to impact outcome.

#### *Efficacy Results—Primary Endpoint*

The primary efficacy analysis of the primary efficacy endpoint showed a statistically significant difference of ALKS 3831 in comparison to placebo, in mean change from baseline in PANSS total score at Week 4. A comparison of olanzapine with placebo suggested a similar treatment effect to ALKS 3831.

**Table 11: Primary Efficacy Results for Change from Baseline in PANSS Total Score at Week 4 (Study A305)**

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

SD: standard deviation; LS Mean=least-squares mean; SE=standard error; CI = confidence interval, not adjusting for multiple comparisons

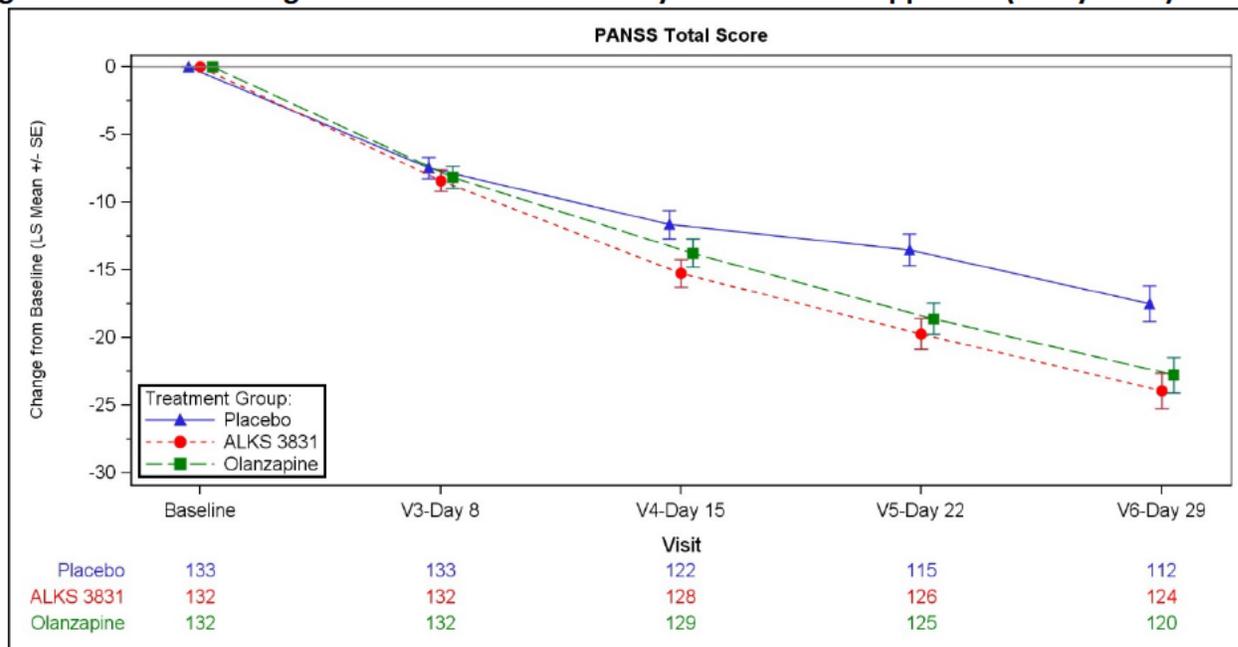
<sup>a</sup>A negative change from baseline indicates improvement.

<sup>b</sup>The corresponding p-value was <0.001.

Source: Table 10 of Applicant’s CSR, verified by FDA statistical reviewer.

The following figure displays the LS mean change from baseline at each visit for each treatment group.

**Figure 6: LS Mean Change from Baseline in PANSS by Visit - MMRM Approach (Study A305)**



PANSS=positive and negative syndrome scale; LS mean=least squares mean; SE=standard error

MMRM=mixed-effects model for repeated measures. The numbers under the graph indicate number of subjects at each time point.

Source: Figure 14.2.1 of Applicant CRS.

**Efficacy Results—Secondary Endpoint**

With respect to the secondary endpoint (change in CGI-S from baseline to Week 4), ALKS 3831

showed a statistically significant difference from placebo, supporting the findings from the primary efficacy endpoint although the observed treatment difference (point estimate = -0.38 and 95% CI =(-0.61, -0.14) was relatively small. Olanzapine also showed similar effects.

**Table 12: CGI-S Change from Baseline to Week 4 (Study A305)**

Treatment Group	Number of Subjects	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
ALKS 3831	132	5.1 (0.7)	-1.2 (0.08)	-0.38 (-0.61, -0.14) <sup>b</sup>
Olanzapine	132	5.1 (0.7)	-1.3 (0.08)	-0.44 (-0.67, -0.20)
Placebo	133	5.1 (0.7)	-0.8 (0.09)	—

SD: standard deviation; LS Mean=least-squares mean; SE=standard error; CI = confidence interval, not adjusting for multiple comparisons

<sup>a</sup>A negative change from baseline indicates improvement.

<sup>b</sup>The corresponding p-value was 0.002.

Source: Table 12 of Applicant's CSR

*Premature Discontinuations and Missing Data*

Overall, nearly 90% of the subjects completed the double-blind phase. The top discontinuation reason was “withdrawal by subject.”

To assess the robustness of the primary analysis of the primary endpoint and impact of missing data, the Applicant performed a sensitivity analysis using a delta-adjusted Pattern Mixture Model. This model incorporated the clinical assumption that ALKS 3831 subjects who discontinued at a given time point would have, on average, their unobserved PANSS worsened by some amount  $\delta$  compared with the observed PANSS of subjects on the same treatment arm who continue to the next time point, and subjects who discontinued from the olanzapine arm would have the same PANSS trajectory as the olanzapine subjects who stay on the study. Shift parameters used in the sensitivity analysis accounted for 10%, 20%, 30%, 40%, and 50% of the observed treatment difference between ALKS 3831 and olanzapine. In this trial, 50% of the observed treatment difference was equivalent to 3.2 points. The sensitivity analysis results were very robust in support of the primary analysis even if the ALKS 3831 dropouts were assumed to have PANSS outcomes worsened, on average, by up to 3.2 points of those of ALKS 3831 subjects whose PANSS scores were collected.

**Table 13: Sensitivity Analysis of PANSS Total Score Change from Baseline– Delta Adjusted Pattern Mixture Model (Study A305)**

Category Statistic <sup>a</sup>	Shift Parameter <sup>b,c</sup>	ALKS 3831
<b>Primary Analysis</b>	0	—
LS Mean Difference vs. Olanzapine <sup>d</sup> (95% CI)	—	-6.4 (-10.0, -2.8)
<i>p</i> -value	—	< 0.001
<b>50% of Treatment Difference between ALKS 3831 and Placebo</b>	3.2	—
LS Mean Difference vs. Placebo (95% CI)	—	-6.6 (-10.3, -2.9)
<i>p</i> -value	—	<0.001

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error

Notes: ALKS 3831 and olanzapine subjects who discontinued would have their unobserved PANSS worsened by some amount delta compared with the observed PANSS of subjects on the same treatment arm who continued to the next time point. Subjects who discontinued from the placebo arm would have the same PANSS trajectory as the placebo subjects who stay on the study.

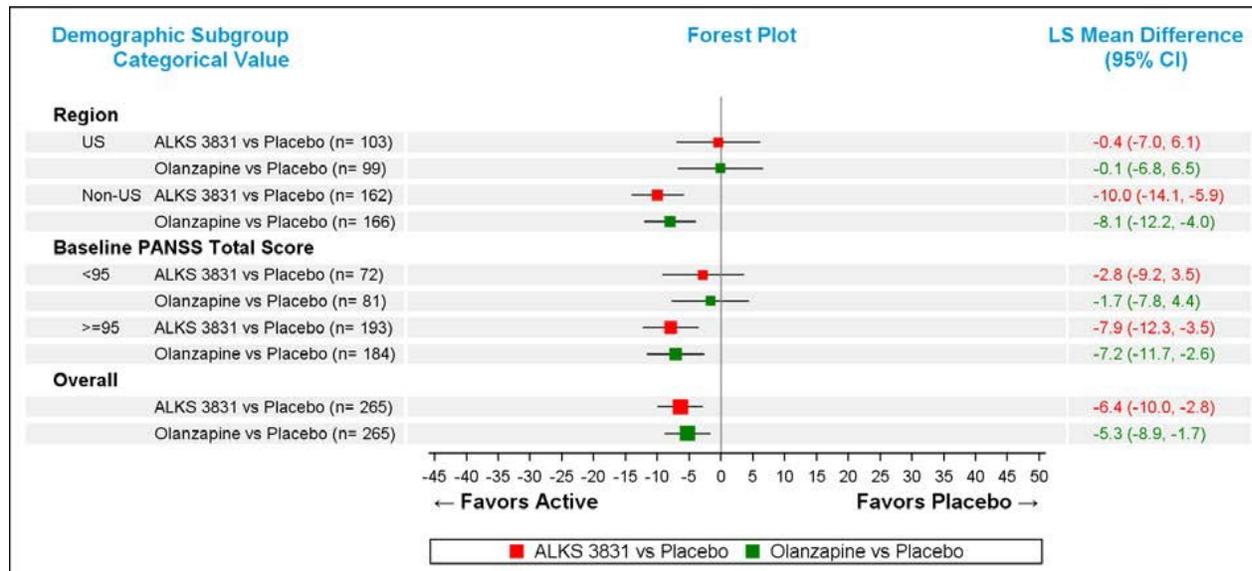
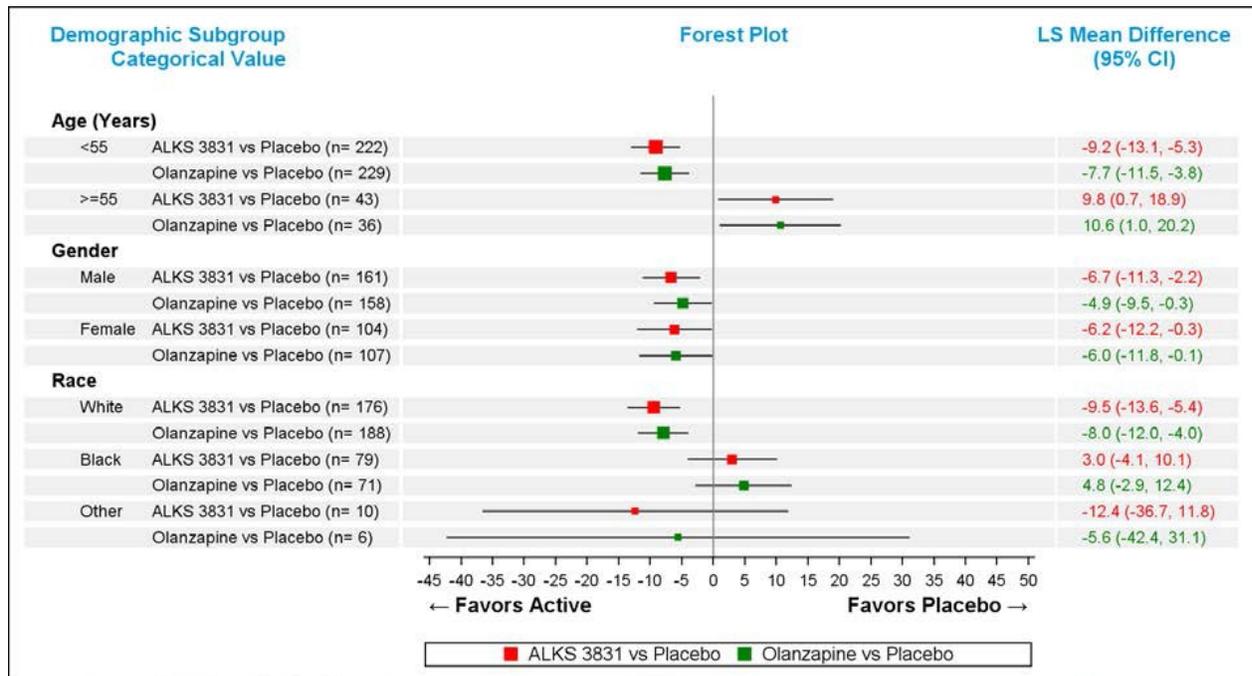
The analysis of covariance (ANCOVA) model with region (U.S. vs non-U.S.) and treatment as factors, and baseline PANSS total score as covariate is used to analyze change from baseline at Week 4. Rubin's rule is used to combine the treatment effect estimates and standard errors across imputations.

Source: extracted from Applicant's CSR, Table 10 and Table 11

*Exploratory Subgroup Analyses on Primary Efficacy Endpoint*

The Applicant reports subgroup analyses results by demographic factors, region, and baseline severity as displayed in the following figure. Although the subgroup analysis suggested a trend in favor of placebo compared to both ALKS 3831 and olanzapine in subjects age >55 years, the age cutoff was arbitrary, and there were very few subjects in this subgroup. In Black subjects, data also suggested a trend slightly in favor of placebo. It is noted that all black subjects were from the United States. In U.S. subjects the observed treatment effects for both ALKS 3831 and olanzapine were essentially neutral. The Applicant believes these findings are consistent with historical findings of decreased antipsychotic treatment response in subjects in the United States.

Figure 7: Forest Plot of Change from Baseline at Week 4 in PANSS by Subgroup (Study A305)



Abbreviations: CI=confidence interval; FAS=full analysis set; PANSS=positive and negative syndrome scale; LS mean= least square mean CI=confidence interval; vs=versus; MMRM=mixed-effects model for repeated measures; US=United States.

Source: Figure 14.2.3 of Applicant's CSR.

**Dose/Dose Response**

Not applicable: Olanzapine doses were flexibly titrated within the approved range of 10 to 20 mg; there was only one dose of samidorphan studied in this trial.

*Durability of Response*

Randomized controlled data beyond 4 weeks are not available. In longer-term open-label (OL) results of completers at Week 52, there was suggested improvement of PANSS scores, especially in subjects originally randomized to placebo as shown below.<sup>17</sup>

**Table 14: PANSS Change from Baseline (Study A306)**

Category Statistics	Placebo /ALKS 3831 (N=74)	ALKS 3831 /ALKS 3831 (N=90)	Olanzapine /ALKS 3831 (N=84)	All Subjects (N=248)
<b>PANSS Total Score</b>				
Baseline, n	74	90	84	248
Mean (SD)	84.6 (20.52)	76.5 (12.53)	76.4 (15.19)	78.9 (16.51)
Week 52, n	56	63	64	183
Mean (SD)	63.5 (11.96)	59.5 (11.17)	61.2 (12.65)	61.3 (11.99)
Change from baseline, mean (SD)	-21.1 (19.93)	-15.6 (11.94)	-12.7 (12.83)	-16.2 (15.41)
P-value	<0.001	<0.001	<0.001	<0.001
Last scheduled on-treatment assessment, n	74	90	84	248
Mean (SD)	65.7 (13.85)	64.1 (14.47)	65.2 (16.27)	64.9 (14.89)
Change from baseline, mean (SD)	-18.9 (21.44)	-12.4 (14.36)	-11.2 (15.98)	-14.0 (17.51)
P-value	<0.001	<0.001	<0.001	<0.001

Source: Clinical Study Report for ALKS3831-A306, Table 9, page 49

CGI-S scores were consistent with PANSS scores: placebo/ALKS 3831 Week 52 mean change from baseline was -1.2 (SD 1.18), ALKS 3831/ALKS 3831 -0.8 (SD 0.72), olanzapine/ALKS 3831 -0.7 (0.77), and all subjects -0.9 (0.92). These data should be interpreted with caution given the nonrandomized, open-label nature and the likelihood of non-responder dropout impacting completer outcomes.

*Persistence of Effect after Drug Discontinuation*

PANSS assessment was not systematically conducted after stopping study drug, so the effect of the drug over time after treatment is stopped or withheld is not evaluable for this trial.

<sup>17</sup> The OL extension study for A305 is Study A306. After participation in A306, subjects can participate in a second, ongoing combined extension study, A308 (which was not reviewed for this application).

## 8.1.2 ALK3831-A303

“A Phase 3 Study to Evaluate Weight Gain of ALKS 3831 Compared to Olanzapine in Adults with Schizophrenia”

### 8.1.2.1 Overview and Objectives (Study A303)

#### *Primary Objective*

To evaluate weight gain with ALKS 3831 compared to olanzapine in adults with schizophrenia

#### *Secondary Objective*

To evaluate the safety and tolerability of ALKS 3831 in adults with schizophrenia

#### *Exploratory Objective*

To evaluate subjects' body composition at Visit 2 and end of treatment

### 8.1.2.2 Trial Design (Study A303)

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 to 55 years who were diagnosed with schizophrenia.

#### *Key inclusion criteria included*

- Age 18 to 55 years
- Schizophrenia per DSM-5 criteria and confirmed using MINI
- Appropriate for outpatient treatment as evidenced by:
  - No hospitalizations for acute exacerbations over the past 6 months
  - PANSS score of 50 to 90
  - CGI-S score of  $\leq 4$
- BMI of 18.0 to 30.0 kg/m<sup>2</sup>
- Stable body weight (no change >5%) over the past 3 months

***FDA Comment:*** Although these inclusion criteria are generally reasonable for an antipsychotic trial in subjects with stable schizophrenia, including only subjects with BMIs up to 30 kg/m<sup>2</sup> (i.e., excluding patients with obesity) limits the generalizability of the results related to weight mitigation.

#### *Key exclusion criteria included*

- Initial onset of active-phase schizophrenia within the past 1 year
- Initiation of first antipsychotic treatment within the past 12 months
- Antipsychotic naive
- History of treatment resistance (failure to respond to two adequate trials of different

antipsychotic medications for a minimum of 4 weeks at the maximum tolerated dose)

- History of poor or inadequate response to olanzapine treatment
- History of clozapine use
- Olanzapine, chlorpromazine, or thioridazine use within the past 6 months
- Long-acting injectable antipsychotic use within the past 6 months with the exception of paliperidone use within the past 12 months
- Electroconvulsive therapy in the past 6 months
- Diagnoses of schizoaffective disorder, bipolar I or II disorder, untreated or unstable major depressive disorder, moderate or severe alcohol or drug use disorder (with the exception of nicotine) within the past 3 months, clinically significant cognitive difficulties within the past 2 years, drug-induced or toxic psychosis, or any other psychiatric condition that could interfere with study participation
- Current suicide risk confirmed by Items 4 or 5 on the C-SSRS
- Clinically significant or unstable medical illness, condition, or disorder that could impact patient safety or efficacy assessment including any gastrointestinal disorder associated with weight loss or, within the past 1 year, any gastrointestinal procedure
- Anorexia nervosa, bulimia nervosa, or binge eating disorder
- Started a smoking cessation program within 6 months or anticipated quitting smoking during the study
- Diabetes mellitus, HbA1c  $\geq 6\%$ , fasting plasma glucose  $\geq 126$  mg/dL
- Fasting total cholesterol  $>280$  mg/dL, fasting TG  $>500$  mg/dL
- Other significant laboratory assessments: AST or ALT  $\geq 2$  times upper limit of normal; ANC  $\leq 1.5 \times 10^3$   $\mu\text{L}$ ; platelet count  $\leq 75 \times 10^3$   $\mu\text{L}$ ; serum creatinine  $>2.5$  mg/dL; positive pregnancy test
- History of weight loss surgery or plan for liposuction during the study
- Joined or planning to join during the study period a weight management program
- Significant dietary or fitness changes within the past 6 weeks
- Positive drug screen for opioids, phencyclidine, amphetamine/methamphetamine, or cocaine
- Opioid agonist use within the past 14 days or anticipated need for such during the study period
- Opioid antagonist use within the past 60 days
- Initiation or dose adjustment of a statin medication within the past 3 months
- Use of any weight loss or hypoglycemic agents

***FDA Comment:*** *Although these exclusion criteria are generally reasonable, excluding patients with diabetes mellitus limits the generalizability of the trial results.*

#### *Randomization and Blinding*

Subjects were randomized in a 1:1 ratio to ALKS 3831 10/10 mg or olanzapine 10 mg.

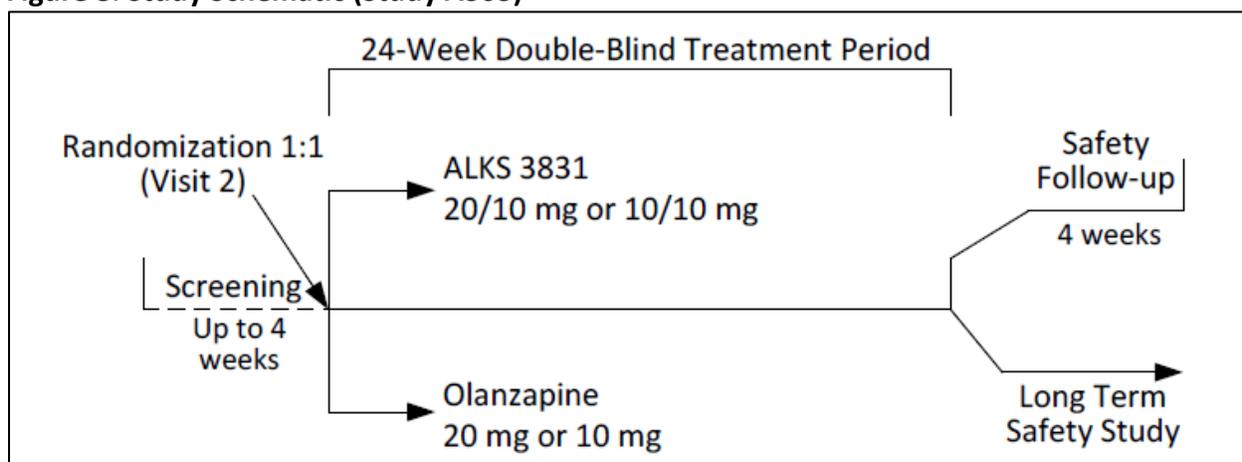
Randomization occurred via an Interactive Web Response System.

Each subject was dispensed weekly or biweekly blister packs beginning at Visit 2, to administer at home each day, preferably at bedtime. Each pack was meant to provide a 7-day supply plus two extra pills. ALKS 3831 and olanzapine were supplied as identical-appearing coated bilayer tablets. Subjects were instructed to keep all unused tablets in their blister card and return unused tablets to the study site at their next visit for adherence review. Study drug samples were not examined by the reviewers.

Study subjects and personnel remained blind to the selected treatment from the time of randomization until database lock.

### Study Schematic

**Figure 8: Study Schematic (Study A303)**



Source: Applicant's Clinical Study Report for ALK3831-A303, Figure 1, page 20

### Dosing

One dose of study drug was to be administered daily, preferably at bedtime. Subjects were to receive ALKS 3831 10/10 mg or olanzapine 10 mg daily from Visit 2 then titrated to 20/10 mg or 20 mg, respectively, daily at the end of Week 1. If the titrated dose was not tolerated, the dose was allowed to be decreased to 10/10 mg or 10 mg, respectively, at the end of Weeks 2, 3, or 4; no other dose changes were permitted beyond Week 4. The doses were selected based on approved lowest and highest olanzapine doses and study data from Study ALKS3831-302.

### Study Schedule

Subjects were randomized after an up to 30-day screening period. Subjects were seen weekly for the first 6 weeks, then biweekly for the remaining 18 weeks. Body weight and waist circumference were measured (in triplicate) at Screening, Baseline, Weeks 1 and 2, and then every 2 to 4 weeks thereafter. Metabolic laboratory parameters were measured at Baseline, Weeks 1, 2, and 4, and every 4 weeks thereafter. Quality-of-Life instruments included the

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IWQOL-Lite and EQ-5D; these were conducted at Baseline and Weeks 4, 12, and 24.

Subjects completing the randomized portion of the trial were eligible to enroll in a long-term safety study (A304). Subjects not continuing in A304 or subjects prematurely discontinuing entered into a 4-week safety follow-up period. The assessment schedule was as follows:

**Table 15: Schedule of Assessments (Study A303)**

Visit	Screening Day -30 to -1	24-Week Double-Blind Treatment																	Safety Follow- up <sup>a</sup>		Monthly Visits <sup>b</sup>
	1	2 <sup>c</sup>	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ET	18	19	20 to 24	
<b>Study Week (Visit Window of ±2 Days for Visits 3-24)</b>			1	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26	28		
<i>Qualification/ Diagnostic Assessments</i>																					
Informed Consent	X																				
Eligibility Criteria Review	X	X																			
Demographics and Medical/ Psychiatric History Review	X																				
MINI	X																				
Height	X																				
<i>Qualification/ Safety Assessments</i>																					
Serology Testing <sup>d</sup>	X																				
Pregnancy Test <sup>e</sup>	X	X								X											
Drug Screen <sup>f</sup>	X	X																			
Physical Exam <sup>g</sup>	X	X															X				
12-lead ECG	X	X								X							X				
AIMS	X	X				X				X							X				
SAS	X	X				X				X							X				
BARS	X	X				X				X							X				
Biochemistry, Urinalysis, and Hematology Samples <sup>h</sup>	X	X	X	X		X			X	X		X		X		X	X				
Vital Signs <sup>i</sup>	X	X	X	X		X		X	X	X		X		X		X	X		X		
Body Weight and Waist Circumference <sup>j</sup>	X	X	X	X		X		X	X	X		X		X		X	X	X	X	X	
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>k</sup>
Concomitant Medication Review <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>m</sup>
C-SSRS <sup>n</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
<i>Psychiatric Efficacy/ Lifestyle/ Quality of Life Assessments</i>																					
PANSS <sup>o</sup>	X	X		X		X		X	X		X		X		X		X				
CGI-S	X	X		X		X		X	X		X		X		X		X				
CGI-I				X		X		X	X		X		X		X		X				
Cigarette Use Questionnaire		X				X		X	X		X		X		X		X				
IWQOL-Lite		X				X					X						X				
EQ-5D-5L		X				X					X						X				
<i>Other/ General Procedures</i>																					
Randomization		X																			
Genotype Sample	X																				
PK Labs <sup>p</sup>		X	X	X		X			X		X		X		X		X				
Study Drug Dispensation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Study Drug Return and Adherence Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Emergency Treatment Card <sup>q</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Source: Applicant’s Clinical Study Report for ALK3831-A303, Table 3, page 34

#### *Study Discontinuation*

Subjects could be removed from the study at any time as determined by the subject, Investigator, or Applicant to be in the best interest of the subject. Any ongoing AEs were to be followed until resolution, deemed stable by the Investigator, or the subject was lost to follow-up.

Following premature discontinuation, subjects could be started on another antipsychotic at the discretion of their prescribing physician. Based on recommendations during development from the DDLO, subjects withdrawn from the study for any reason were asked to return to the clinic for an early termination (ET) visit, scheduled as close as possible to the subject's last dose. Subjects who discontinued study drug but were willing to come in for further assessments were asked to complete the ET visit followed by two safety follow-up visits 2 and 4 weeks after the ET visit, and monthly thereafter, until end of planned treatment, to collect weight and adverse events and record the use of new antipsychotics.

#### *Prohibited Medications*

The following medications were not permitted during the study:

- Any other antipsychotic unless the subject was being actively tapered off
- Any other psychotropic medications with the exception of at least 30-day stable dose of:
  - Antidepressants
  - Benzodiazepines to treat sleep symptoms
  - Beta blockers, antihistamines, and anticholinergics to treat extrapyramidal symptoms
- Varenicline although nicotine replacement patch and gum were permitted
- Any prescription or over-the-counter weight reduction medication
- Systemic steroids
- Topiramate
- Calcitonin
- Diabetes treatment and hypoglycemic agents
- Medications contraindicated with olanzapine or exhibited drug-interaction potential
- Moderate-to-strong cytochrome P450 3A4 inducers or inhibitors within 30 days before randomization through follow-up
- Opioid agonists within 14 days before screening
- Opioid antagonists within 60 days before screening

#### *Treatment Compliance*

Study personnel monitored treatment adherence with scheduled drug accountability records for the amount of study drug dispensed versus the amount returned.

#### *Data Quality Assurance*

The protocol, Investigator's Brochure, electronic case report form instructions, and AE reporting procedure were reviewed with the Investigator or designee at each site, and trainings were

conducted at each site initiation visit and during region-specific Investigator Meetings. Data was recorded onto appropriate source documents according to GCP procedures and entered into the EDC system, which maintained a full audit trail. An Alkermes monitor or designee reviewed source records on site and compared them to eCRF data. Laboratory results and ECGs were transferred electronically from the central laboratories to the EDC database. AEs were coded using MedDRA 21.0; prior and concomitant medications were categorized using the World Health Organization Anatomical Therapeutic Chemical drug dictionary, Enhanced Extended with Herbal version WHODRUG 16.

A study center was audited for report of potential data falsification; adjudication determined there was no data falsification or general misconduct at the site.

### 8.1.2.3 Endpoints (Study A303)

Reviewers from DDLO were involved as consultants in meetings with the primary review division and the Applicant regarding this pivotal trial and relevant study endpoints. The Applicant was informed that weight should be the primary measure in a trial comparing ALKS 3831 to olanzapine (in other words, assessing whether the addition of samidorphan to olanzapine would mitigate the weight gain associated with olanzapine treatment). DDLO reviewers recommended that the mitigation of weight gain with olanzapine could be shown with co-primary<sup>18</sup> endpoints: (1) evaluating mean weight change from baseline, and (2) utilizing a categorical/responder analysis of proportion of patients in each group with a clinically relevant change in weight from baseline, an approach similar to the design of studies for obesity drugs<sup>19</sup> to demonstrate clinically meaningful weight loss. 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.

#### *Co-Primary Endpoints*

- Percent change in body weight from baseline to Week 24
- Proportion of subjects with  $\geq 10\%$  weight gain at Week 24

#### *Secondary Endpoint*

- Proportion of subjects with  $\geq 7\%$  weight gain at Week 24

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<sup>18</sup> Statistical significance needs to be demonstrated on both primary endpoints to support an efficacy claim.

<sup>19</sup> 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 if on categorical analysis, at least two times more patients 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*.

#### *Other Endpoints*

- Percent change from baseline body weight in the Early Weight Gain population at Week 24
- Proportion of subjects with  $\geq 10\%$  weight gain in the Early Weight Gain population at Week 24
- Change from baseline in fasting lipids, glucose, insulin, and HbA1c by visit
- Absolute change in body weight by visit
- Change from baseline in waist circumference by visit
- Change from baseline in PANSS total score and subscales by visit
- Change from baseline in CGI-S by visit
- CGI-I score by visit
- Change from baseline in IWQOL-Lite total score and subscales by visit
- Change from baseline in EQ-5D-5L score by visit

#### **8.1.2.4 Statistical Analysis Plan (Study A303)**

##### *Sample size considerations*

- The initial target sample size was 200 randomized subjects per treatment group (400 in total). This was expected to provide at least 90% power to detect a 4% difference (3% on ALKS 3831 versus 7% on olanzapine with standard deviation of 9%) in percent weight gain and 13% difference (14% on ALKS 3831 versus 27% on olanzapine) in proportion of subjects with  $\geq 10\%$  weight gain at Week 24 between treatment groups.
- An unblinded interim analysis was prespecified for sample size re-estimation. The timing for performing the interim analysis was when 50% of the initially planned sample size had completed or prematurely discontinued. The sample size increase was based on the conditional power calculated using the interim data. Based on the conditional power, it would be assigned into one of three zones: favorable ( $CP \geq 90\%$ ), promising ( $30\% \leq CP < 90\%$ ), or unfavorable ( $CP < 30\%$ ). The target sample size of 200 per arm will be increased to 270 subjects per arm when the conditional power for at least one co-primary endpoint is in the promising zone and neither of the primary endpoints are in the unfavorable zone.

##### *Analysis populations*

###### Safety Population

Safety population included subjects who were randomized and received at least one dose of study drug.

###### FAS Population

The FAS was defined as all subjects who were randomized, received at least one dose of study drug, and had at least one post-baseline weight assessment. The FAS was used for efficacy analysis.

#### Additional Populations Studied

- Early Weight Gain Population—FAS subjects who gained any weight at Week 1
- Stage 1—the first 200 FAS subjects who had completed or discontinued prematurely before the interim analysis
- Stage 2—FAS subjects who had completed or discontinued prematurely after the interim analysis

#### *Primary Analysis*

- The primary analysis model for the first co-primary was ANCOVA with baseline weight as a covariate and the factors of Treatment group, Age group, and Race. The primary analysis model for the second co-primary and the secondary endpoints was a logistic regression model with baseline weight as a covariate and the factors of Treatment group, Age group, and Race. Age group consists of subjects <30 years of age and >30 years of age. Race consists of Black or African American, and non-Black or Non-African American.
- The missing data were imputed using the Multiple Imputation (MI) method, under an assumption of missing observations being missing at random. This imputation method assumes the weight measurement of early discontinued subjects at Week 24 has the same distribution as Week 24 completers. Before obtaining efficacy estimates for each stage, missing data at Week 24 were imputed with MI method. For any subject whose missing data pattern was non-monotonic (defined as having missing data in between visits), the Markov Chain Monte Carlo method was used to impute the data to a monotonic missing pattern. Next, the missing data were imputed sequentially by each visit using a regression method. The imputation regression model included treatment group, race (Black or African American, Non-Black or Non-African American) and baseline age (<30, ≥30 years) as factors, and body weight at all previous visits (including baseline weight) as covariates. Per pre-specification, a missing observation was imputed 500 times. Thus, obtained were 500 primary analysis datasets, each of which consists of Week 24 observed weight measurements of the completers and imputed weight values of the dropouts for their missing observations. The primary analysis model was applied to each of the datasets to obtain efficacy estimates and their relevant statistics. These 500 estimates were analyzed with proc mianalyze (SAS) to obtain the final estimate of the efficacy effect for each stage.

#### *Hypothesis Test and Treatment Effect Estimates*

To guard against the potential Type I error inflation resulting from sample size increase, the p-values for the two co-primary endpoints were mainly derived from the CHW<sup>20</sup> test statistic. This test statistic combines the Z test statistics from two stages (before and after the interim analysis) with a pre-specified fixed weight assigned to each stage based on the original sample

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<sup>20</sup> A method proposed by Cui, Hung, and Wang. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55:853-857.

size. The Applicant used the conventional test statistic (not adjusted for sample size increase) to derive the p-value for all other efficacy endpoints. Confidence intervals for all efficacy endpoints were not adjusted for sample size increase.

#### *Multiplicity Adjustment*

Since ALKS 3831 has to be statistically significantly better than olanzapine on both co-primary endpoints for the study to be claimed positive, no multiplicity adjustment is needed, in the sense that each co-primary endpoint can be tested at a full significance level (that is,  $\alpha = 0.05$ ). Testing of the secondary endpoint will proceed at the same alpha level if the trial is concluded to be positive.

#### *Sensitivity Analyses for Missing Data*

To assess the robustness of the primary analysis with respect to missing data, the Applicant pre-specified several sensitivity analyses, including:

- The delta-adjusted Pattern Mixture Model. This approach is to assess the potential impact of missing data due to missing not at random (MNAR). It incorporates the clinical assumption that olanzapine subjects who discontinue at a given time point would have, on average, their unobserved weight gain decreased by some amount  $\delta$  compared with the observed weight gain of subjects in the olanzapine arm who continue to the next time point, while ALKS 3831 subjects who discontinue would have the same weight gain trajectory as the ALKS 3831 subjects that stay on the study.
- Repeating the primary analysis but including both on- and off-treatment weight assessments after premature discontinuation of study drug. In the primary analysis, off-treatment weight assessments were not included.
- Analysis based on mixed model with repeated measurements (MMRM) model. The MMRM model will include treatment, visit, treatment-by-visit interaction term, race and age as categorical fixed effects, and baseline weight as a covariate. An unstructured covariance structure will be applied. The analysis will be performed on all observed post-randomization on-treatment weight measurements without imputation of missing data.

#### **8.1.2.5 Protocol Amendments**

Five protocol amendments occurred after the original protocol was finalized on September 17, 2015.

##### *Amendment 1: December 15, 2015*

The key secondary endpoint “proportion of subjects with  $\geq 10\%$  weight gain at Week 24” was changed to a co-primary endpoint.

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*Amendment 2: August 11, 2016*

- An independent statistical center conducted an unblinded interim analysis to determine final sample size.
- Antipsychotic naive subjects were added to exclusion criteria.
- PK sampling included measurement of all samidorphan metabolites.

*Amendment 3: January 10, 2017*

The interim and final statistical analyses were modified to control for type I error, and a body composition substudy was added.

*Amendment 4: May 4, 2017*

Two key secondary endpoints were added assessing the Early Weight Gain population—body weight change percent from baseline and proportion of subjects with  $\geq 10\%$  weight gain.

*Amendment 5: September 18, 2018*

- Multiple imputation and MMRM without imputation would be utilized, instead of last observation carried forward.
- The “key secondary endpoints” of assessing the Early Weight Gain population (body weight change percent and proportion of subjects with  $\geq 10\%$  gain) were changed to “other endpoints.”
- Fasting insulin change from baseline was added to metabolic effect assessments.

There were two SAP amendments but none after database lock.

### **8.1.2.6 Results (Study A303)**

*Compliance with Good Clinical Practices*

The Applicant conducted this study in accordance with Good Clinical Practices principles, the International Conference on Harmonization Guidelines E6, and local regulations. Thirteen audits were conducted at 12 sites. All protocols and amendments were reviewed by each clinical site’s Institutional Review Board. An attestation was included in Section 5 of the CSR.

*Financial Disclosure*

The study was conducted at 64 sites total in the United States. Eight principal investigators and two subinvestigators reported financial disclosures, consisting of a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, honoraria, or significant equity interest. See Appendix 17.2 for more details. Study design minimizes potential bias because it was a randomized, blinded trial with objective endpoints.

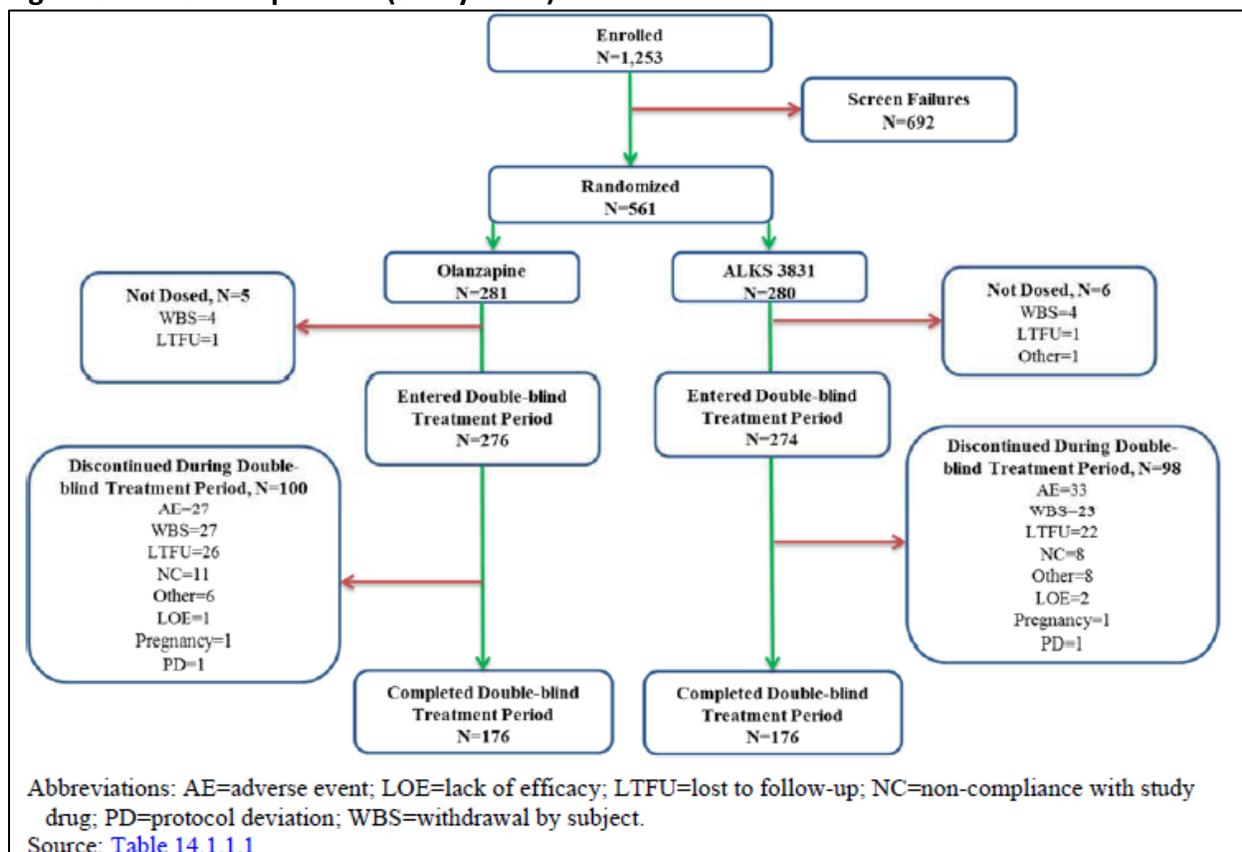
*Data Quality and Integrity*

Datasets appeared to be of good quality and were complete. The Applicant responded to clarifying questions within an acceptable timeframe. The reviewers have no concerns about data integrity.

*Patient Disposition*

There were 1,253 subjects screened for the study. Initially the planned total number of randomized subjects was 400. As a result of the unblinded interim analysis, the decision was made to increase the sample size to 540. Eventually, 561 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. The Early Weight Gain Population consisted of 371 subjects who gained weight at Week 1. There were 352 subjects (64%) who completed the study: 35.8% of subjects discontinued in the ALKS group and 36.2% in the olanzapine group. 10.9% of subjects discontinued because of AEs; 9.1% of subjects withdrew; and 8.7% of subjects were lost to follow-up. The treatment arms were evenly distributed with similar rates of discontinuation in the ALKS 3831 and olanzapine treatment arms; rates of discontinuation because of AEs were slightly higher in the ALKS 3831 group (12.0% compared to olanzapine group 9.8%).

**Figure 9: Patient Disposition (Study A303)**



Source: Applicant’s Clinical Study Report for ALK3831-A303, Figure 2, page 54

**Table 16: Subject Population by Treatment (Study A303)**

Category	Olanzapine	ALKS 3831	All Subjects
Subjects in Safety Population <sup>a</sup> , N	276	274	550
Subjects in Full Analysis Set Population <sup>b</sup> , N	272	266	538
Subjects in Early Weight Gain Population <sup>c</sup> , N	194	177	371
Subjects Who Completed Double-blind Treatment Period, n (%)	176 (63.8)	176 (64.2)	352 (64.0)
Subjects Who Discontinued Double-blind Treatment Period, n (%)	100 (36.2)	98 (35.8)	198 (36.0)
Reasons for Treatment Discontinuation, n (%)			
Adverse Event	27 (9.8)	33 (12.0)	60 (10.9)
Withdrawal by Subject	27 (9.8)	23 (8.4)	50 (9.1)
Lost to Follow-up	26 (9.4)	22 (8.0)	48 (8.7)
Non-Compliance with Study Drug	11 (4.0)	8 (2.9)	19 (3.5)
Other	6 (2.2)	8 (2.9)	14 (2.5)
Lack of Efficacy	1 (0.4)	2 (0.7)	3 (0.5)
Pregnancy	1 (0.4)	1 (0.4)	2 (0.4)
Protocol Deviation	1 (0.4)	1 (0.4)	2 (0.4)
Subject Who Continued into Long-term Safety Extension Study, n	133	133	266
Subjects Who Entered the Monthly Visit <sup>d</sup> , n (%)	20 (7.2)	25 (9.1)	45 (8.2)
Subjects Who Completed the Monthly Visit <sup>d</sup> , n (%)	12 (4.3)	12 (4.4)	24 (4.4)

Note: Percentages are based on the subjects in the Safety Population in each column (N).

<sup>a</sup> The Safety Population includes all randomized subjects who received at least 1 dose of study drug.

<sup>b</sup> The FAS includes all subjects in the Safety Population who have at least 1 postbaseline weight assessment.

<sup>c</sup> The early weight gain population includes all subjects in the FAS Population who gain weight (>0 kg) at Week 1.

<sup>d</sup> After completing the early termination visit and safety follow-up visits, randomized subjects who prematurely discontinue study drug can enter into monthly visits until end of their planned treatment to collect their weight, adverse events, and new antipsychotics.

Source: Table 14.1.1.1, Applicant Clinical Study Report

### *Protocol Violations/Deviations*

In this study, 29 subjects (5.3%) had “important” protocol deviations (15 receiving ALKS and 14 receiving olanzapine). The deviations included not meeting inclusion/exclusion criteria (<1%), study drug non-compliance defined as taking <70% specified amount of medication (1.3%), and receiving prohibited medications (3.6%). There were similar small numbers of protocol deviations between the two treatment groups, so these were not likely to have markedly affected efficacy results.

### *Demographic Characteristics*

In overall enrollment, there was a higher percentage of black males; other minority representation was inadequate and lower than their rates in the general population so this

study's findings may be of limited generalizability to those groups. Slight male preponderance is typical for a population with schizophrenia. Demographic characteristics were reasonably balanced across treatment groups as were baseline weight parameters.

**Table 17: Demographic Characteristics (Study A303)**

	ALKS 3831 (N=266)	Olanzapine (N=272)	Total (N=538)
<b>Sex, n (%)</b>			
Male	188 (71)	203 (75)	391 (73)
Female	78 (29)	69 (25)	147 (27)
<b>Age</b>			
Mean years (SD)	40.3 (9.82)	40.1 (10.05)	40.2 (9.93)
Median (years)	42	40	41
Min, max (years)	19, 55	18, 55	18, 55
<b>Race, n (%)</b>			
White	61 (23)	64 (24)	125 (23)
Black or African American	193 (73)	190 (70)	383 (71)
Asian	4 (2)	4 (2)	8 (2)
American Indian or Alaska Native	2 (1)	2 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	1 (<1)
Other	2 (1)	4 (2)	6 (1)
Multiple races	3 (1)	8 (3)	11 (2)
<b>Ethnicity, n (%)</b>			
Hispanic or Latino	36 (14)	41 (15)	77 (14)
Not Hispanic or Latino	230 (86)	231 (85)	461 (86)

Source: A303 CSR, Table 14.1.3.2.1

*Other Baseline Characteristics*

The majority of patients in the trial were overweight, with a mean BMI of 25.4 kg/m<sup>2</sup>. Mean IWQOL-Lite and EQ-5D-5L scores (higher values for both instruments indicate a better quality-of-life) were similar among groups at baseline.

**Table 18. Baseline Parameters – Efficacy Population (Study A303)**

	ALKS 3831 (N=266)	Olanzapine (N=272)	Total (N=538)
<b>Height</b>			
Mean cm (SD)	173.94 (9.303)	173.96 (9.262)	173.95 (9.274)
Median (cm)	174.95	173.45	174.00
Min, max (cm)	148.0, 196.0	150.0, 201.1	148.0, 201.1
<b>Weight</b>			
Mean kg (SD)	77.00 (13.680)	77.45 (13.478)	77.23 (13.568)
Median (kg)	76.75	76.60	76.65
Min, max (kg)	40.6, 112.6	46.1, 115.5	40.6, 115.5
<b>Body Mass Index</b>			
Mean kg/m <sup>2</sup> (SD)	25.31 (3.137)	25.48 (3.194)	25.40 (3.164)
Median (kg/m <sup>2</sup> )	25.70	26.10	25.90

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Min, max (kg/m <sup>2</sup> )	17.9, 29.9	18.0, 30.0	17.9, 30.0
<b>Body Mass Index Group</b>			
Underweight (<18.5); n(%)	5 (2)	1 (<1)	6 (1)
Normal (18.5 to <25); n(%)	115 (43)	114 (42)	229 (43)
Overweight (25 to <30); n(%)	146 (55)	155 (57)	301 (56)
Obese (≥30); n(%)	0	2 (1)	2 (<1)
<b>IWQOL-Lite Total Score</b>			
Mean (SD)	89.6 (15.12)	88.0 (15.31)	88.8 (15.22)
Median	96.4	95.2	95.6
Min, max	13, 100	26, 100	13, 100
<b>EQ-5D-5L Index Score</b>			
Mean (SD)	0.84 (0.160)	0.83 (0.154)	0.84 (0.157)
Median	0.86	0.84	0.85
Min, max	0.3, 1.0	0.2, 1.0	0.2, 1.0

Source: A303 CSR, Table 14.1.3.2.1

Rates of baseline medical and psychiatric morbidity were similar between treatment groups. In the Safety Population, approximately 17% of subjects had a history of anxiety, 15% had a history of hypertension, and 11% had a history of depression.

*Treatment Compliance, Concomitant Medications, and Rescue Medication Use*

Among patients who were on-treatment and without missing data, mean study drug adherence was 96.2% in the ALKS 3831 group and 97.2% in the olanzapine group.

**Table 19. Treatment Adherence During Double-Blind Period – Safety Population (Study A303)**

	ALKS 3831 (N=274) n (%)	Olanzapine (N=276) n (%)
<b>Treatment Adherence (%)<sup>a</sup></b>		
N <sup>b</sup>	269	275
Mean (SD)	96.2 (9.18)	97.2 (6.03)
Median	99.0	99.0
Min, Max	29, 102	50, 111
<b>Treatment Adherence Category, n (%)<sup>c</sup></b>		
<70%	5 (1.8)	2 (0.7)
≥70% to 79%	4 (1.5)	5 (1.8)
≥80% to 89%	18 (6.6)	12 (4.3)
≥90% to 100%	234 (85.4)	244 (88.4)
>100%	8 (2.9)	12 (4.3)

<sup>a</sup>Treatment adherence (%) = 100 x (Total tablets taken) / Total tablets subject should have taken from the first dose date to the last dose date of study drug, inclusive, during the Double-blind Treatment Period.

<sup>b</sup>Six subjects were reported as having taken the study drug, but they did not return any dispensed pills; therefore, their treatment adherence results were missing.

<sup>c</sup>The treatment adherence category is based on the adherence rate rounded to the nearest integer.

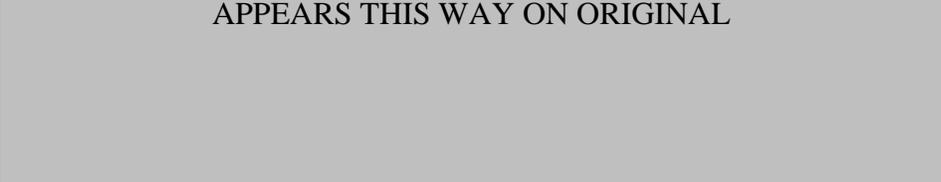
Source: A303 CSR, Table 8

As noted in the protocol description, olanzapine dose was titrated from 10 mg to 20 mg after 1 week; olanzapine could be titrated down to 10 mg at the end of weeks 2, 3, or 4

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if there were tolerability issues, at the discretion of the Investigator. No further dose adjustments were allowed beyond Week 4. Overall, mean dose of olanzapine was similar between treatment groups (Table 20).

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**Table 20: Summary of Olanzapine Dose, Safety Population (Study A303)**

	ALKS 3831 N=274	OLZ N=276
<b>Overall Mean Dose of OLZ (mg/day)<sup>a</sup></b>		
n	269	275
Mean (SD)	16.8 (3.94)	16.9 (3.57)
Median	19.0	19.0
Min, Max	4, 20	8, 20
<b>Modal Dose of OLZ (mg/day)<sup>b</sup></b>		
n	269	275
Mean (SD)	17.8 (4.17)	17.7 (4.19)
Median	20.0	20.0
Min, Max	10, 20	10, 20
<b>At Week 4<sup>c</sup></b>		
Low Dose, n/m (%)	34/228 (14.9)	47/243 (19.3)
High Dose, n/m (%)	194/228 (85.1)	196/243 (80.7)
<b>Final Dose of OLZ<sup>c</sup></b>		
Low Dose, n/m (%)	57/269 (21.2)	54/275 (19.6)
High Dose, n/m (%)	212/269 (78.8)	221/275 (80.4)

Note: Six subjects were reported as having taken the study drug, but they did not return any dispensed pills; therefore, their olanzapine dose levels were missing; no further dose adjustments allowed beyond Visit 6 (Week 4), and the dose remained fixed for the remaining 20 weeks of the study.

<sup>a</sup>Overall mean dose of olanzapine is calculated as time-weighted average of olanzapine dose level during the entire study.

<sup>b</sup>Modal dose is defined as the most frequent dose level during the entire study.

<sup>c</sup>Low dose: 10 mg of olanzapine for Olanzapine Group or ALKS 3831 10/10 mg for ALKS 3831 treatment group.

High dose: 20 mg of olanzapine for Olanzapine Group or ALKS 3831 20/10 mg for ALKS 3831 treatment group.

Source: A303 CSR, Table 24

A total of 85.5% of study subjects took at least one prior medication. Prior medications used by at least 10% of subjects in the ALKS 3831 or olanzapine groups, respectively, included risperidone (33.6%, 30.4%), quetiapine fumarate (15.7%, 17.8%), aripiprazole (8.8%, 13.0%), trazodone (10.6%, 9.8%), and benztropine mesylate (8.0%, 10.1%).

During the double-blind treatment period, a similar proportion of subjects in each treatment group was treated with concomitant antipsychotic medications (ALKS 3831 24.1% and olanzapine 24.3%); however, when excluding the first 2-week tapering period, only one (0.4%) and three (1.1%) subjects, respectively, were started on any *new* antipsychotic medication.

Finally, in order to interpret missing data due to study drug discontinuation, understanding antipsychotic treatment of subjects after study drug discontinuation is informative. Risperidone and quetiapine were the most frequently used antipsychotics in these subjects (both have modest weight gain in comparison to olanzapine), and their use was generally similar among randomized groups (Table 21).

**Table 21: Listing of Concomitant Antipsychotic Medications Started After Treatment Discontinuation, Safety Population (Study A303)**

	ALKS 3831 N=98 %	OLZ N=100 %
Subjects who took at least one antipsychotic medication after treatment discontinuation	37	34
Risperidone	15	12
Quetiapine fumarate	9	9
Haloperidol	5	3
Lurisdone hydrochloride	4	3
Olanzapine	4	3
Quetiapine	3	2
Paliperidone	2	1
Chlorpromazine	1	0
Loxapine	1	0
Aripiprazole	0	4
Asenapine maleate	0	1
Fluphenazine	0	1
Ziprasidone hydrochloride	0	1

Source: Response to Agency Request for Information dated May7, 2020: Part 2, Table Q3.3

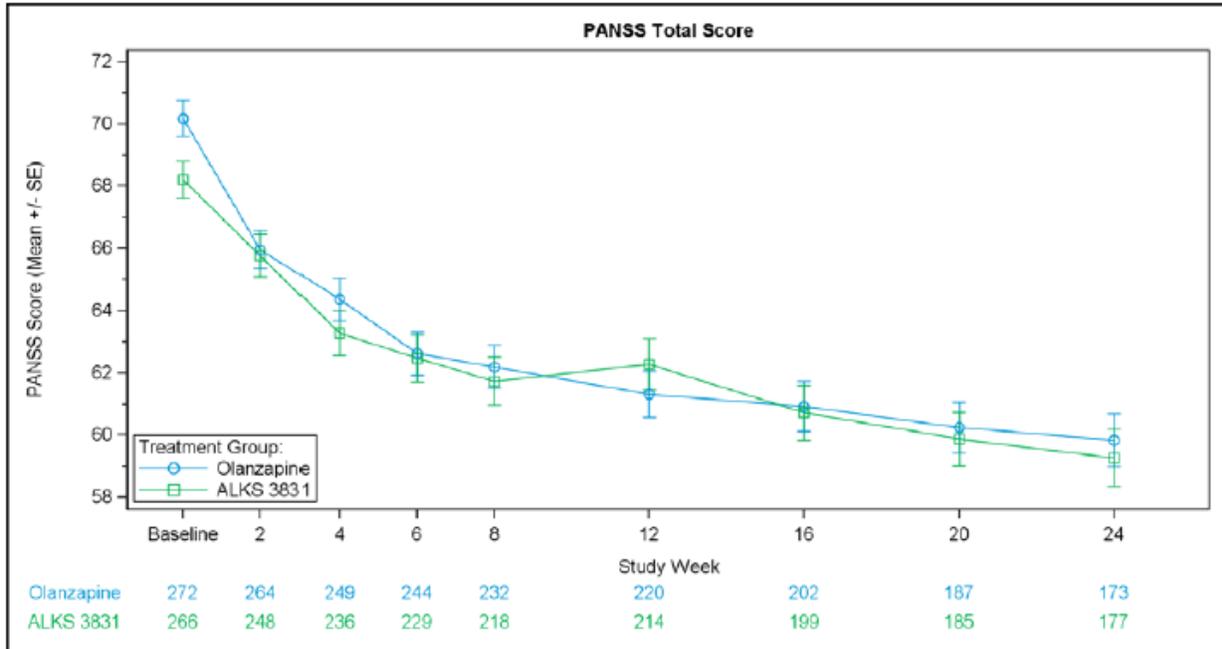
***Efficacy Results***

The co-primary and key secondary endpoints assessed weight gain mitigation. See Section 8.2.3.1 for analysis of these endpoints. This section will address the exploratory antipsychotic endpoints.

*Exploratory Antipsychotic Endpoints*

Compared to the olanzapine group, the ALKS 3831 group experienced similar improvements in PANSS total and subscale scores, in CGI-S scores, and in CGI-I scores. Comparison of scores at baseline and Week 24 are presented in the subsequent figures.

**Figure 10: PANSS Change from Baseline (Study A303)**

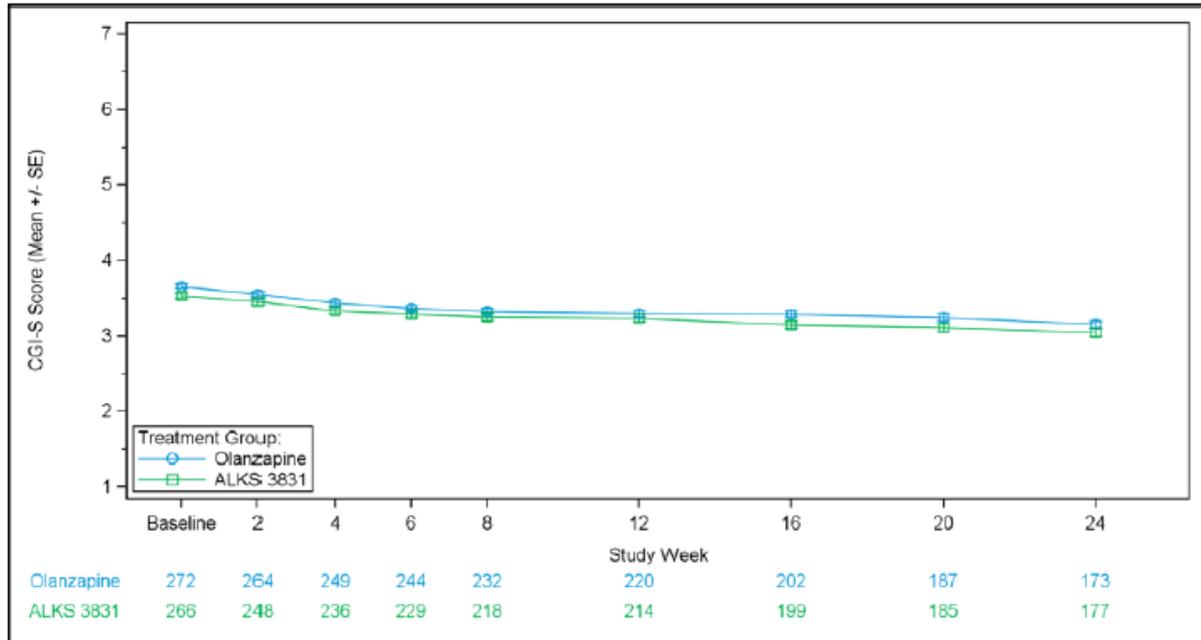


Abbreviations: FAS= full analysis set; PANSS=positive and negative syndrome scale; SE=standard error.

Note: The numbers in the bottom rows indicate the numbers of subjects with assessment at each visit.

Source: Applicant's Clinical Study Report for ALKS3831-A303, Figure 22, page 93

**Figure 11: CGI-S Change from Baseline (Study A303)**



Abbreviations: CGI-S=Clinical Global Impression-Severity; FAS=full analysis set; SE=standard error.  
 Note: The numbers in the bottom rows indicate the numbers of subjects with assessment at each visit.

Source: Applicant’s Clinical Study Report for ALKS3831-A303, Figure 26, page 95

*Dose/Dose Response*

Not applicable: Olanzapine doses were flexibly titrated within the approved range of 10 to 20 mg; there was only one dose of samidorphan studied in this trial.

*Durability of Response*

Randomized controlled data beyond 24 weeks are not available. In the longer-term OL extension study (A304), there was suggested stability of PANSS scores as shown below.<sup>21</sup>

<sup>21</sup> The OL extension study for A303 is Study A304. After participation in A304, subjects can participate in a second, ongoing combined extension study, A308 (which was not reviewed for this application).

**Table 22: PANSS Change from Baseline (Study A304)**

Visit Statistics	ALKS 3831/ ALKS 3831 (N=132)	OLZ/ ALKS 3831 (N=133)	All Subjects (N=265)
<b>PANSS Total Score</b>			
Baseline, n	132	133	265
Mean (SD)	58.6 (12.34)	59.5 (11.23)	59.0 (11.78)
Median	57.5	60.0	59.0
Min, Max	37, 96	38, 91	37, 96
V27-Week 52, Change from Baseline, n	87	81	168
Mean (SD)	0.1 (7.96)	-0.6 (9.05)	-0.2 (8.48)
Median	-1.0	-1.0	-1.0
Min, Max	-18, 29	-25, 27	-25, 29

Source: Applicant’s Clinical Study Report for ALKS3831-A304, Table 11, page 47

*Persistence of Effect after Drug Discontinuation*

PANSS assessment was not systematically conducted after stopping study drug, so the effect of the drug over time after treatment is stopped or withheld is not evaluable for this trial.

**8.1.3 ALKS3831-302**

“A Phase 2, Randomized, Multicenter, Safety, Tolerability, and Dose-Ranging Study of Samidorphan, a Component of ALKS 3831, in Adults with Schizophrenia Treated with Olanzapine”

**8.1.3.1 Overview and Objectives (Study 302)**

The objectives of this study were to investigate ALKS 3831’s safety, tolerability, and dose-ranging. Efficacy evaluations were considered exploratory and investigated whether the ALKS 3831 effect (when all three doses were pooled) was equivalent to olanzapine.

**8.1.3.2 Trial Design (Study 302)**

This was a phase 2, randomized, placebo-controlled, multicenter study in subjects with schizophrenia who had not been exposed to certain antipsychotics within the past year. The study was conducted in two parts:

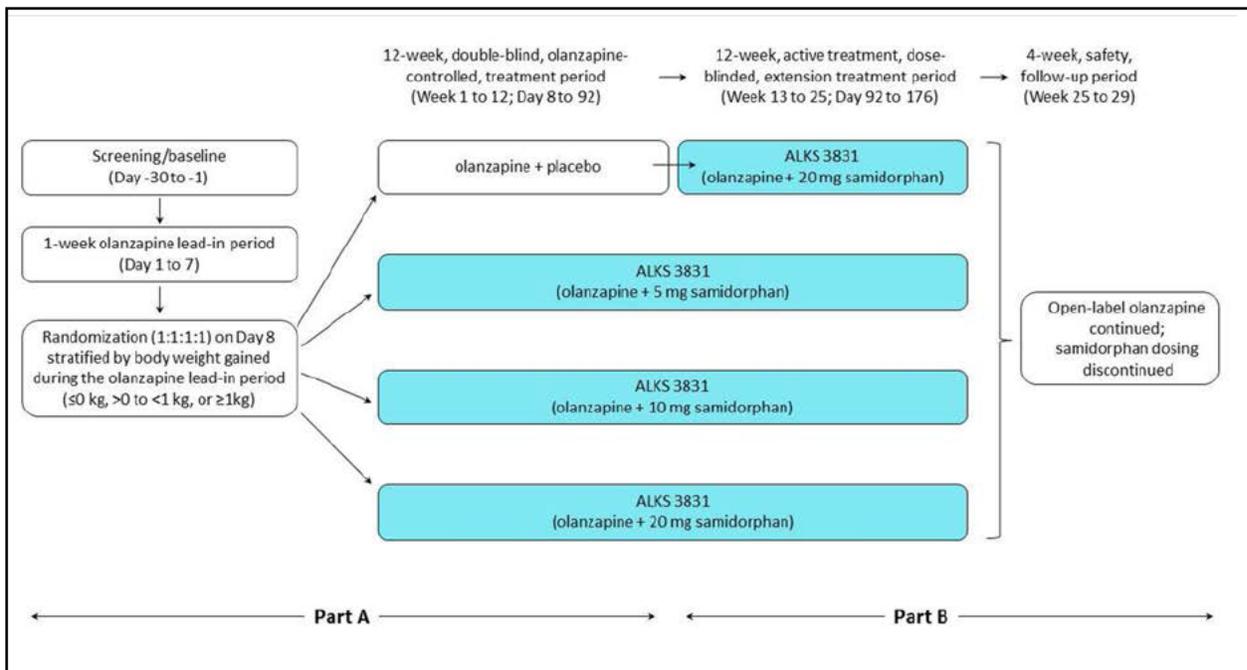
- Part A included a screening period, a 1-week olanzapine lead-in period, and a 12-week double-blind, olanzapine-controlled treatment period. According to the Applicant, the “1-week olanzapine lead-in design element was employed to enhance the ability to detect an

effect of weight, since it is known that those who gain weight early on with olanzapine treatment are more likely to gain weight overall.” Subjects who completed the lead-in period were randomized in a 1:1:1:1 ratio to receive either olanzapine only (olanzapine + placebo) or one of the three ALKS 3831 treatment groups (olanzapine + 5, 10, or 20 mg samidorphan). Randomization was stratified by the amount of weight change during the olanzapine lead-in period:  $\leq 0$  kg,  $>0$  to  $<1$  kg, or  $\geq 1$  kg. Subjects who were taking antipsychotic medication 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 ALKS 3831 (still in their blinded groups), followed by a 4-week safety period with uninterrupted olanzapine dosing, including two follow-up safety visits.

This review focused on results from Part A.

**Figure 12: Study Schematic (Study 302)**



Source: 302 CSR, Figure 1

Selected eligibility criteria were:

**Key inclusion criteria**

- Age 18 to 50 years
- BMI 17 to 30 kg/m<sup>2</sup>
- Schizophrenia diagnosis, clinically stable

- Stable exercise routine and body weight

*Key exclusion criteria*

- Comorbid neuropsychiatric disorders
- Moderate or severe alcohol or drug use disorder
- Positive HIV status
- Diabetes, or any of the following:
  - Hemoglobin A1c (HbA1c)  $\geq 6.5\%$
  - Fasting plasma glucose (FPG)  $\geq 126$  mg/dL
  - Random plasma glucose  $\geq 200$  mg/dL
- Clinically significant or unstable medical condition, for example:
  - Hypotension/hypertension not stabilized by medical therapy
  - Unstable thyroid dysfunction in the past 6 months
  - Personal or family history of neuroleptic malignant syndrome
  - Total cholesterol  $>280$  mg/dL or TG  $> 500$  mg/dL
  - Inflammatory bowel disease or other GI disorder associated with weight loss
  - Anorexia nervosa, bulimia nervosa, or binge eating disorder
  - Neurologic conditions such as seizures, brain tumor, subdural hematoma, head trauma, CNS infection, stroke
- Cardiac conditions such as arrhythmia, cardiomyopathy, myocardial infarction, unstable angina, ECG abnormality, prolonged QT
- Clinically significant abnormal laboratory values
- Pregnant or breastfeeding
- GI surgery within 1 year, has had a surgical procedure for weight loss
- Smoking cessation program within 6 months
- Used olanzapine, clozapine, mesoridazine, chlorpromazine, or thioridazine for more than 1 week during the past year or at any time during the past 3 months
- Statin started or dose changed within 3 months

### **8.1.3.3 Endpoints (Study 302)**

The primary efficacy endpoint was change in PANSS total score. Weight- and metabolic-related endpoints were exploratory in nature.

*Exploratory Weight-related Endpoints*

- Percent change in body weight
- Absolute change in body weight
- Proportion of subjects with weight gain  $\geq 7\%$

*Additional Weight-related Exploratory Endpoints*

- Change in waist circumference

- Change in IWQOL-Lite scales (physical function, self-esteem, sexual life, public distress, work) and total score

#### **8.1.3.4 Statistical Analysis Plan (Study 302)**

##### *Sample size consideration*

The calculations were based on the primary efficacy endpoint assuming an equivalence margin of 10 points, a standard deviation of 20 points, and a true difference of 0 points. With these assumptions, 280 randomized subjects were expected to provide 95% power to demonstrate equivalence between drugs on the primary endpoint. These 280 subjects represent 70 subjects for each treatment arm (ALKS 3831 5 mg, ALKS 3831 10 mg, ALKS 3831 20 mg, and placebo) in a 1:1:1:1 ratio. For the primary analysis, subjects in the three ALKS 3831 treatment groups were pooled for comparison with olanzapine. If this analysis shows equivalence, follow-up analyses on individual dose levels will be performed. Assuming a 20% discontinuation rate prior to randomization, an estimated 350 subjects will be enrolled in this study.

The efficacy analysis was conducted on two analysis populations:

- The 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 included all FAS 1 subjects who gained weight during the initial week of olanzapine treatment prior to randomization and had at least one post-baseline weight assessment

FAS 1 population was the primary population for analyses of all efficacy variables, but note that efficacy evaluations were considered exploratory.

##### *Primary analysis*

- The primary analysis was to assess whether the effect of pooled ALKS 3831 (when all three doses were pooled) were equivalent to that of olanzapine based on a pre-specified equivalence margin of 10 points. If this analysis shows equivalence, similar analyses on individual dose levels will be performed.
- The primary analysis model was based on mixed-model for repeated measures MMRM model. The model will include variables for weight change strata in the olanzapine lead-in period, treatment group, visit, and treatment group-by-visit interaction term as categorical fixed effect; baseline value will be included as a covariate. The covariance structure will AR(1). Missing data will not be imputed.

*Analyses of exploratory weight endpoints*

The analysis method was analogous to that for the primary efficacy endpoint. For binary outcomes, a Cochran-Mantel-Haenszel (CMH) option was used to make adjustments for the olanzapine lead-in period weight change strata.

***FDA Comment:*** *This was an exploratory phase 2 study. We consider all analyses purely exploratory. There has not been an established equivalence margin to demonstrate the equivalence of one drug to another for a psychiatric disorder.*

**8.1.3.5 Protocol Amendments (Study 302)**

There were two protocol amendments; important changes are noted below.

*Amendment 1: June 5, 2013*

- The objective of the assessment of the safety and tolerability of ALKS 3831 was moved ahead of the impact of samidorphan on weight and other metabolic factors, and the primary endpoint was changed to number and percentage of subjects with adverse events from randomization to the end of Part A with percent change in body weight moved to a secondary endpoint
- A 4-week follow-up period after Part B was added in which olanzapine would be continued without samidorphan
- The extent of the accumulated safety data for the data and safety monitoring board (DSMB) meeting was clarified
- DEXA for assessment of body composition was removed
- Two follow-up visits were added for patients who prematurely discontinued during Part A
- Weight change from screening to Visit 2 was not to be more than 1 kg
- Plasma sample collections for pharmacokinetics (PK) were clarified

*Amendment 2: February 26, 2014*

- The objective of ALKS 3831 as a treatment of schizophrenia was placed first, and the primary endpoint was changed to the absolute change in PANSS total score from randomization to the end of Part A
- The sample size was decreased from 400 to 280 subjects (based on absolute change in PANSS total score)

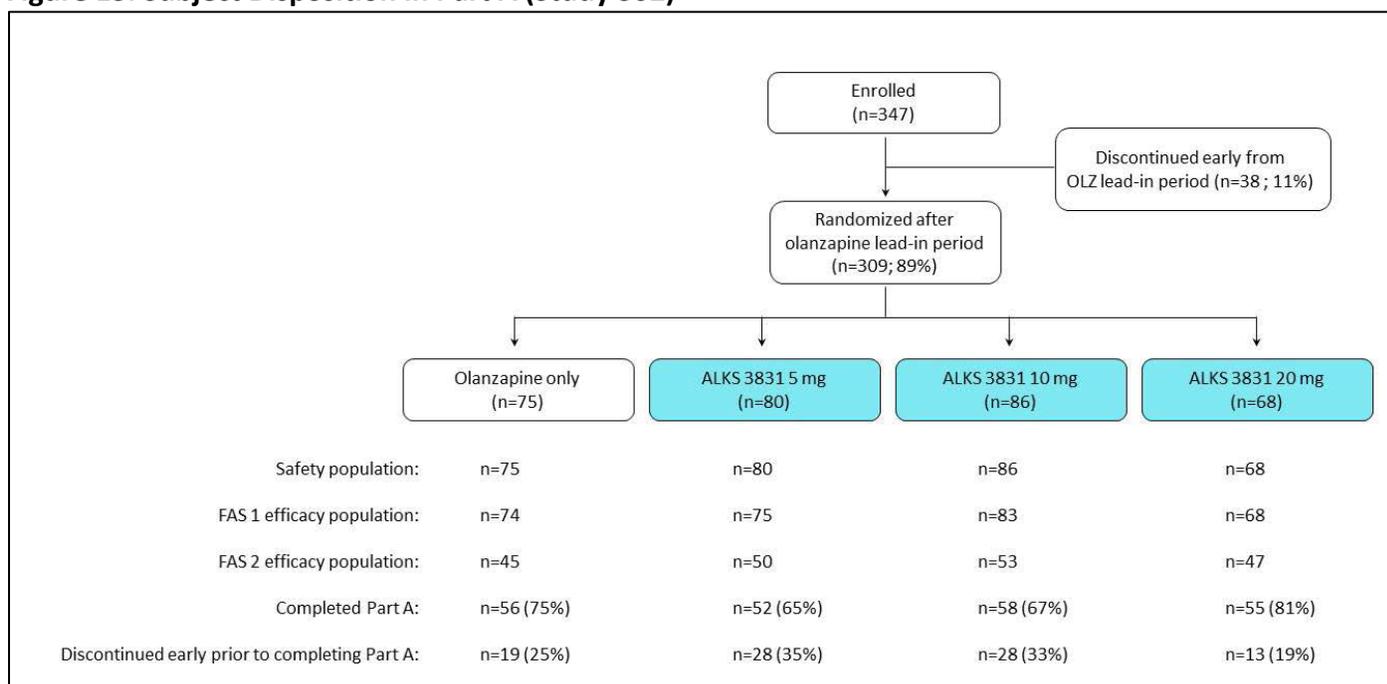
- Metabolic assessments were specified as safety assessments (rather than efficacy): blood pressure, lipids, fasting glucose and insulin, and HbA1c
- FAS 1 and FAS 2 populations were defined

### 8.1.3.6 Results (Study 302)

#### Patient Disposition

A summary of the disposition of subjects in Part A of the trial is shown in the figure below:

**Figure 13. Subject Disposition in Part A (Study 302)**



Source: 302 CSR, Figure 3

Most discontinuations during the lead-in period were due to withdrawal by the subjects, protocol violations, or subjects who were lost-to-follow-up.

In the randomized, controlled portion of the trial (Part A), the largest proportion of discontinuations in the olanzapine + placebo arm was due to loss to follow-up (12.0%), whereas the majority of patients in the olanzapine + samidorphan arms discontinued due to withdrawal by subject (9.4%) and adverse events (9.0%).

Of the 221 subjects who completed Part A, 218 enrolled into the Part B extension phase. In Part B, subjects who had previously received olanzapine-only switched to ALKS 3831 20 mg (n=54), and subjects who had previously received ALKS 3831 continued with their assigned treatment: ALKS 3831 5 mg (n=52), ALKS 3831 10 mg (n=57), and ALKS 3831 20 mg (n=55).

Overall, of the 218 patients enrolled in Part B, 187 (85.8%) completed Part B.

*Protocol Violations/Deviations*

The majority of protocol violations in Part A were due to poor treatment compliance (4 subjects on olanzapine + placebo and 6 on olanzapine + samidorphan). Two subjects on olanzapine + samidorphan were administered contraindicated medications after randomization (haloperidol and quetiapine) and one subject had a positive urine drug screen (not specified) at screening.

*Demographic and Other Baseline Characteristics*

The majority of subjects in the FAS 1 efficacy population in this trial were male (74%), black or African American (61.3%), not Hispanic or Latino (94.3%), and residing in the United States (84%). Demographics were well-balanced among groups.

In the FAS 1 population overall, mean BMI was 25.1 kg/m<sup>2</sup>, mean height was 174.0 cm, and mean weight was 76.3 kg. These mean values were similar among treatment groups.

**Table 23: Demographic and Other Baseline Characteristics (Study 302)**

	Olanzapine + Placebo (N=74) n (%)	Olanzapine + Samidorphan (N=226)			Total (N=300) n (%)
		+Samidorphan 5 mg (N=75) n (%)	+ Samidorphan 10 mg (N=83) n (%)	+ Samidorphan 20 mg (N=68) n (%)	
<b>Sex</b>					
Male	52 (70.3)	57 (76.0)	63 (75.9)	50 (73.5)	222 (74.0)
Female	22 (29.7)	18 (24.0)	20 (24.1)	18 (26.5)	78 (26.0)
<b>Age, years</b>					
Mean (SD)	40.2 (8.19)	38.1 (8.55)	38.0 (7.96)	39.3 (8.38)	38.9 (8.27)
Median	41.5	39.0	39.0	41.0	40.0
Min, max	18, 50	18, 50	20, 50	20, 50	18, 50
<b>Race</b>					
White	28 (37.8)	23 (30.7)	34 (41.0)	23 (33.8)	108 (36.0)
Black or African American	43 (58.1)	51 (68.0)	48 (57.8)	42 (61.8)	184 (61.3)
Asian	1 (1.4)	0	1 (1.2)	2 (2.9)	4 (1.3)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	2 (2.7)	0	0	1 (1.5)	3 (1.0)
<b>Ethnicity</b>					
Hispanic or Latino	4 (5.4)	5 (6.7)	5 (6.0)	3 (4.4)	17 (5.7)
Not Hispanic or Latino	70 (94.6)	70 (93.3)	78 (94.0)	65 (95.6)	283 (94.3)
<b>Region</b>					
United States	59 (79.7)	65 (86.7)	68 (81.9)	60 (88.2)	252 (84.0)
Rest of the World	15 (20.3)	10 (13.3)	15 (18.1)	8 (11.8)	48 (16.0)
<b>Height, cm</b>					
Mean (SD)	173.5 (80.9)	173.8 (10.82)	174.7 (10.37)	174.1 (9.99)	174.0 (9.85)
Median	172.9	175.3	176.0	174.0	175.0
Min, max	155, 192	149, 201	151, 199	150, 193	149, 201
<b>Weight, kg</b>					

	Olanzapine + Placebo (N=74) n (%)	Olanzapine + Samidorphan (N=226)			Total (N=300) n (%)
		+Samidorphan 5 mg (N=75) n (%)	+ Samidorphan 10 mg (N=83) n (%)	+ Samidorphan 20 mg (N=68) n (%)	
Mean (SD)	75.6 (12.38)	77.4 (13.22)	76.8 (13.75)	75.4 (12.81)	76.3 (13.04)
Median	77.3	76.1	75.1	75.6	76.1
Min, max	51, 104	45, 102	47, 115	49, 98	45, 115
<b>BMI, kg/m<sup>2</sup></b>					
Mean (SD)	25.1 (3.42)	25.6 (3.22)	25.1 (3.26)	24.8 (3.41)	25.1 (3.32)
Median	25.8	26.0	25.0	25.2	25.6
Min, max	18, 30	19, 30	18, 30	18, 30	18, 30
<b>BMI Group</b>					
Underweight (<18.5)	1 (1.4)	0	1 (1.2)	1 (1.5)	3 (1.0)
Normal (18.5 to <25)	32 (43.2)	30 (40.0)	40 (48.2)	32 (47.1)	134 (44.7)
Overweight (25 to <30)	41 (55.4)	42 (56.0)	42 (50.6)	34 (50.0)	159 (53.0)
Obese (≥30)	0	3 (4.0)	0	1 (1.5)	4 (1.3)

Source: 302 CSR, Table 14.1.2.2.E

#### *Treatment Compliance, Concomitant Medications, and Rescue Medication Use*

In the safety population, the mean compliance with samidorphan/placebo was 97.6% and similar across groups; 95.8% of subjects demonstrated a compliance of at least 80%. As olanzapine was locally sourced through sites or a pharmacy card was provided, drug accountability data were not available for olanzapine.

No subjects were started on concomitant antipsychotic medications during the double-blind on-treatment Part A period, and one subject (1.9%) in the OLZ/OLZ+SAM 20 mg group was started on quetiapine during the double-blind on-treatment Part B period.

After treatment discontinuation from Part A, a higher proportion of subjects randomized to ALKS 3831 (29%) were started on antipsychotic medications (primarily aripiprazole, haloperidol, and quetiapine) than randomized to olanzapine (11%).

#### *Efficacy Results—Primary Endpoint*

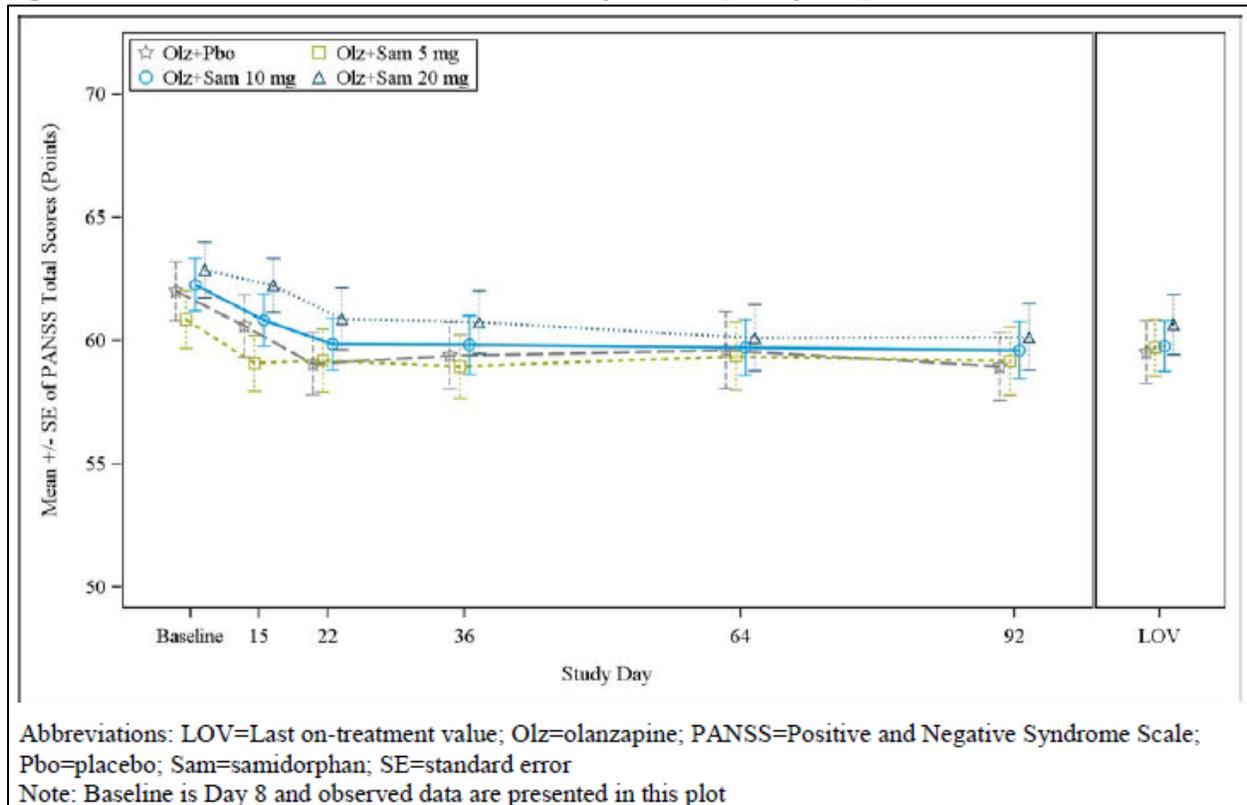
Treatment with olanzapine plus samidorphan was associated with similar change in schizophrenia symptoms as olanzapine plus placebo and was within the equivalence margin selected by the Applicant. Over the 12-week double-blind period, the LS mean change in PANSS total score in the pooled olanzapine plus 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.

**Table 24: PANSS Total Score (Study 302, Part A)**

	Olanzapine+ Placebo (N=74)	Olanzapine +Samidorphan			Any Samidorphan (N=226)
		Samidorphan 5 mg (N=75)	Samidorphan 10 mg (N=83)	Samidorphan 20 mg (N=68)	
Baseline, mean (SD)	62.0 (10.42)	60.9 (10.04)	62.3 (9.64)	62.9 (9.37)	62.0 (9.68)
Change from baseline to Day 92, mean (SD)	-3.0 (7.40)	-1.3 (6.45)	-2.7 (6.66)	-2.6 (10.59)	-2.3 (8.10)
LS mean (SE) change from baseline to Day 92	-2.9 (0.82)	-1.5 (0.85)	-2.7 (0.79)	-2.5 (0.83)	-2.2 (0.47)
95% CI of LS mean	(-4.5, -1.3)	(-3.2, 0.1)	(-4.2, -1.1)	(-4.2, -0.9)	(-3.2, -1.3)
LS mean Difference (SE) vs. Olz+Pbo	—	1.3 (1.18)	0.2 (1.13)	0.3 (1.17)	0.6 (0.94)
95% CI of LS mean difference	—	(-1.0, 3.6)	(-2.0, 2.5)	(-2.0, 2.6)	(-1.2, 2.5)

Source: Clinical Study Report for ALK3831-302, Figures 14 and 15, pages 78 and 80

**Figure 14: PANSS Total Score, Part A FAS 1 Population (Study 302)**



Source: Clinical Study Report for ALK3831-302, Figure 5, page 81

CGI-S scores remained stable as well: ALKS 3831/ALKS 3831 Week 52 mean change from baseline -0.03 (SD 0.469), olanzapine/ALKS 3831 -0.20 (0.563), and all subjects -0.11 (0.521). These data should be interpreted with caution given the nonrandomized, open-label nature and the likelihood of non-responder dropout impacting completer outcomes.

#### *Persistence of Effect after Drug Discontinuation*

PANSS assessment was not systematically conducted after stopping study drug, so the effect of the drug over time after treatment is stopped or withheld is not evaluable for this trial.

### **8.1.4 Integrated Assessment of Antipsychotic Effectiveness Across Trials**

In Study A305, the pivotal randomized, double-blind, and controlled study evaluating subjects with an acute exacerbation of schizophrenia, treatment with ALKS 3831 was associated with improvement in symptoms. The LS mean change from baseline 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 with a 95% CI (-10.2, -2.8). These primary findings were corroborated by CGI-S changes from baseline.

Subgroup analysis is noteworthy in suggesting a trend in favor of placebo compared to both ALKS 3831 and olanzapine in subjects age >55 years; however, the age cutoff was arbitrary, and there were very few subjects in this subgroup. In Black/African American subjects, data also suggested a trend slightly in favor of placebo. In U.S. subjects, the observed treatment effects for both ALKS 3831 and olanzapine were essentially neutral. The latter two subgroups are linked because all Black/African American subjects were from the United States, and most U.S. subjects were Black/African American. The Applicant believes these findings are consistent with historical findings of decreased antipsychotic treatment response in subjects in the United States.

In Study A303, antipsychotic efficacy was not a primary nor a secondary endpoint; however, efficacy was supported by LS mean change from baseline PANSS total scores of -8.2 (SE=0.73) in the ALKS 3831 group and -9.4 (SE=0.72) in the olanzapine group. These findings were corroborated by CGI-S changes from baseline.

In Study 302, a proof-of-concept study, treatment with olanzapine plus samidorphan was associated with similar change in schizophrenia symptoms compared to olanzapine plus placebo. 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.

## **8.2 Review of Safety**

### **8.2.1 Safety Review Approach**

This safety review will examine adult subjects with schizophrenia in the ALKS 3831 clinical trial program. There will be a focused review on weight mitigation and cardiometabolic effects in Study A303 with supportive analysis of relevant data in Studies 302, A304, and A306. For the general safety review, each of the two pivotal studies, A305 and A303, will be analyzed separately as, because of varying durations and randomization arms, a pooling strategy would not provide meaningful results. Supportive phase 2 Study 302 and the two long-term open-label studies, A304 and A306, were also briefly reviewed for pertinent information, although the latter lacked controlled safety data. I also briefly reviewed the results of the ALKS 3831 phase 1, 2, and 3 programs in the Integrated Summary of Safety and 120-Day Safety Update for any major trends or concerns.

### **8.2.2 Review of the Submitted Safety Database**

#### **8.2.2.1 Overall Exposure**

Per the Applicant, a total of 18 clinical studies evaluating single and multiple doses of ALKS 3831

were either completed or ongoing as of the 120-Day Safety Update cutoff date of October 17, 2019. Additionally, a total of nine clinical studies evaluating single and multiple doses of samidorphan alone were completed. A total of 1,601 subjects received at least one dose of ALKS 3831 in the entire development program (this does not include data from Study A307 which is ongoing with data not yet unblinded), and 557 have received at least one dose of samidorphan alone. Completed phase 2 and 3 studies provide a total exposure of 1,022 patient-years. Studies A307, a short-term controlled trial in subjects with early disease, and A308, a long-term open-label trial, are ongoing.

**Table 25: Safety Population for ALKS 3831 Development (N=2004)**

	ALKS 3831 (n=1,601)	Olanzapine (n=288)	Placebo (n=115)
Healthy volunteers <sup>a</sup>	238	81	29
Controlled trials conducted for this indication	408	186	46
All other trials conducted for this indication <sup>a</sup>	955	21	40
Controlled trials conducted for other indications	0	0	0

<sup>a</sup>Subjects enrolled in a crossover study or a subsequent extension study were counted once, preferentially in the ALKS 3831 group.

Source: Applicant response to IR June 3, 2020

**Table 26: Safety Population for Samidorphan Development (N=724)**

	Samidorphan (n=557)	Placebo (n=167)
Healthy volunteers <sup>a</sup>	221	29
Controlled trials conducted for this indication	0	0
All other trials conducted for this indication	0	0
Controlled trials conducted for other indications	336	138

<sup>a</sup>Subjects enrolled in a crossover study or a subsequent extension study were counted once, preferentially in the samidorphan group.

Source: Applicant response to IR June 3, 2020

**Table 27: Duration of ALKS 3831 Exposure**

Samidorphan Dose	Number of subjects exposed to ALKS 3831				
	>= 1 dose <sup>a</sup>	>=4 weeks	>=6 months	>=12 months	>=18 months
5 mg	80	63	39	0	0
10 mg	1161	827	589	423	279
20 mg	177	111	35	0	0
30 mg	54	0	0	0	0

<sup>a</sup>Subjects enrolled in a crossover study receiving multiple dosages of ALKS 3831 with various dosages of samidorphan are listed for each dose they received.

Source: Applicant response to IR June 3, 2020

**Table 28: Duration of Samidorphan Exposure**

Samidorphan Dose	Number of subjects exposed to samidorphan alone				
	>= 1 dose <sup>a</sup>	>=4 weeks	>=6 months	>=12 months	>=18 months
1 mg	104	87	0	0	0
2.5 mg	100	83	0	0	0
10 mg	132	100	0	0	0

<sup>a</sup>Subjects enrolled in a crossover study receiving multiple dosages of samidorphan are listed for each dose they received.

Source: Applicant response to IR June 3, 2020

### 8.2.2.2 Relevant Characteristics of the Safety Population:

The safety populations in Studies A305 and A303 generally shared the same demographic characteristics as the FAS populations discussed in the efficacy section and appear generally appropriate for a population with schizophrenia. Study A305 was conducted internationally, and Study A303 was conducted in the United States. Both studies enrolled a reasonably standard range of adult subjects with schizophrenia ages 18 to 67 years. Minority representation was better than most clinical trials for black subjects, but the proportions of non-black minorities and females were less than in the general U.S. population and in patients with schizophrenia. Because of exclusion criteria, the study populations may have slightly healthier subjects with fewer psychiatric and medical comorbidities and with less use of concomitant medication than those who would use the drug in the general population. Disease severity is likely comparable to the general population with schizophrenia requiring pharmacological treatment, as verified by PANSS score cutoffs. For both studies, the safety population included all subjects who were randomized and received at least one dose of study drug. A total of 403 adults were randomized and 401 were dosed in Study A305, with 352 (87.8%) completers and 49 subjects (12.2%) who discontinued. A total of 561 adults were randomized and 550 were dosed in Study A303, with 352 (64%) completers and 198 subjects (36%) who discontinued.

### 8.2.2.3 Adequacy of the Safety Database:

The trial population numbers are acceptable for meeting the regulatory exposure requirements for this NDA: ICH E1 drug exposure recommendations are 300 subjects for 6 months and 100 subjects for 1 year. The total number of subjects exposed for  $\geq 6$  months was 663 subjects and for  $\geq 1$  year was 423 subjects.

The treatment periods in these trials ranged from 14 days to 24 weeks for the short-term trials, which appears adequate to assess short-term treatment effects and safety. The long-term trial treatment periods ranged from 52 weeks to 208 weeks.

#### Data Quality

In Study 302, after the database lock and prior to unblinding of the study team, it was noted Subject (b) (6) (from the olanzapine/samidorphane 20 mg group) had abnormal fluctuations in body weight from Day 50 to Day 64; see below.

Figure 15: Listing of Body Weights from Subject (b) (6) (Study 302)

Subject ID	Treatment Group	Visit	Visit Date (Study Day)	Weight (median) (kg)	Change in Body Weight	
					Change from Day 1	Change from Baseline (Day 8)
(b) (6)	olanzapine/oliz+Sam 20 mg/oliz+Sam 20 mg	Day 10	(b) (6) (10)	97.8	0.74	0
		Day 15	(15)	97.6	0.54	-0.2
		Day 22	(22)	98.2	1.14	0.4
		Day 29	(30)	99.02	1.96	1.22
		Day 36	(36)	99.4	2.34	1.6
		Day 50	(50)	99.4	2.34	1.6
		Day 64	(66)	119.5	22.44	21.7
		Day 78	(79)	118.1	21.04	20.3
		Day 92	(92)	118.1	21.04	20.3
		Day 93	(93)	118.1	21.04	20.3
		Day 94	(94)	118.1	21.04	20.3
		Day 99	(100)	118.1	21.04	20.3
		Day 106	(107)	118.6	21.54	20.8
		Day 113	(115)	118.1	21.04	20.3
		Day 120	(122)	120.4	23.34	22.6
		Day 134	(136)	118.1	21.04	20.3
		Day 148	(150)	118	20.94	20.2
		Day 162	(164)	99.8	2.74	2
		Day 176	(178)	99.9	2.84	2.1
		Day 190	(191)	99.6	2.54	1.8
	Day 204	(205)	99.6	2.54	1.8	

Source: 302 CSR, Listing 16.2.4.2

The Applicant stated that as a result of the reported data anomalies, a site audit was conducted by Alkermes Clinical Quality Assurance (QA) to investigate the incident further. The Investigator and the site's QA Director also conducted an internal investigation following the Alkermes site audit and confirmed to Alkermes that the Study Coordinator falsified data and admitted to unauthorized changes to the clinical trial weight and date data for Subject (b) (6) for Visits 11-25. As a result, the employee was removed from the study and the weight data for Subject (b) (6) was excluded in the analysis. According to the Applicant, the investigation revealed that no other subject data from this site was impacted.

#### 8.2.2.4 Adequacy of Applicant's Clinical Safety Assessments

##### *Issues Regarding Data Integrity and Submission Quality*

No major concerns about data integrity were noted by the OCS Core Data Fitness team. OSI inspection concluded inspected clinical data at the respective sites appeared reliable overall (see Section 4.1).

##### *Categorization of Adverse Events*

I performed some AE analysis adjustment varying from the Applicant's analyses for my tables in Section 8.2.3. (Applicant AE data tables were used for the other sections; please refer to the source under each table, as needed.) For all studies, I classified Treatment-Emergent AEs (TEAEs) as any AE that occurred after at least one dose during the treatment period. The studies used MedDRA versions 19 in Study A305 and 21 in Study A303 to code AEs. AEs were recorded at each study visit for all studies, and the Applicant appeared to use standard methods for severity coding. I inspected verbatim and preferred terms and agreed with most of the Applicant's mapping. I used my own clinical judgment and reviewed available data and narratives for AE adjudication apart from those the Applicant included.

I grouped the following terms together:

Schizophrenia: auditory hallucination, psychotic symptom, psychotic disorder, catatonia

Fatigue: lethargy, asthenia, sluggishness

Somnolence: sedation, sedation complication, hypersomnolence

Mental status change: disorientation, depressed level of consciousness

Agitation: anger, irritability

Abdominal pain: gastritis, abdominal pain upper, gastrointestinal pain

Restlessness: feeling jittery

Bradykinesia: psychomotor retardation

Dyslipidemia: hyperlipidemia, blood cholesterol increased, hypercholesterolemia, low density lipoprotein increased, blood triglycerides increased, hypertriglyceridemia

Heart rate increased: tachycardia

Blood pressure increased: hypertension

Blood glucose increased: hyperglycemia, diabetes mellitus

Blood insulin increased: hyperinsulinemia

Neutrophil count decreased: neutropenia

White blood cell count decreased: leukopenia

Blood prolactin increased: hyperprolactinemia

Liver function test abnormal: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased

Increased appetite: food craving

Drug abuse: substance use, substance-induced psychotic disorder

Depression: depressed mood, depressed symptom

Hyperhidrosis: cold sweat, night sweats

Muscle spasms: muscle twitching

Extra dose administered: accidental overdose

Urine analysis abnormal: WBCs urine positive, protein urine positive, urine bilirubin increased (note, glycosuria was not included)

Sexual dysfunction: libido decreased, libido increased, erectile dysfunction, anorgasmia

Hemoglobin decreased: anemia

Additionally, various specific terms were combined under the following categorical terms as appropriate: upper respiratory infection, lower respiratory infection, infection, musculoskeletal pain, and musculoskeletal injury.

#### *Adverse Events of Special Interest*

The study protocols did include specially prompted AE assessments for particular AEs of special interest: extrapyramidal symptoms (EPS), suicidality, and drug abuse, dependence, or withdrawal. Additional safety assessment scales administered in both studies included:

1. Abnormal Involuntary Movement Scale (AIMS)
2. Barnes Akathisia Rating Scale (BARS)
3. Simpson Angus Scale (SAS)

These are clinician-administered tools to assess and track extrapyramidal symptoms throughout the study. The results will be discussed in Section 8.2.7.

4. C-SSRS

This is a clinician-administered tool to assess and track suicidal ideation and behavior throughout the study. The results will be discussed in Section 8.2.7.

#### *Routine Clinical Tests*

Studies A305 and A303 both included a standard array of serum chemistry, hematology, urinalysis, vital sign, and ECG assessments. Study A305 was conducted inpatient for 2 to 4 weeks; for subjects discharged at 2 weeks, they were followed weekly for the remaining 2 weeks of study. For those who did not enroll in the long-term extension study, this was followed by a 2-week follow-up. Study A303 had weekly visits for the first 6 weeks then biweekly for the remaining 18 weeks of study. For those who did not enroll in the long-term extension study, this was followed by a 4-week follow-up.

#### Blood Chemistries

Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin, Blood Urea Nitrogen, Calcium, Chloride, Creatinine, Creatine Phosphokinase (CK), Gamma-Glutamyl Transferase (GGT), Glucose, Hemoglobin A1c (HbA1c), Insulin, Lactate Dehydrogenase (LDH), Potassium, Prolactin, Protein, Sodium, Uric Acid

Clinical/Statistical Review  
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Lybalvi (Olanzapine/Samidorphane, ALKS 3831)

#### Lipid Panel

LDL-Cholesterol, HDL-Cholesterol, Total Cholesterol, Triglycerides

#### Hematology

Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC Total Count, WBC Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

#### Urinalysis

Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

#### Thyroid Function Panel

Thyroid Stimulating Hormone (TSH) - if TSH abnormal, Free T3 and Free T4 performed

#### Urine Drug Screening

Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Cotinine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone, Tricyclic Antidepressants

#### Other Tests

Breath Alcohol Test and, in female subjects of child-bearing potential, Serum and Urine Pregnancy Tests (beta-hCG)

### **8.2.3 Weight Mitigation Study Results**

#### **8.2.3.1 ALK3831-A303**

This was a phase 3, multicenter, 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. See Section 8.1.3 for a description of study design, and patient population disposition and characteristics.

#### *Efficacy Results—Co-Primary Endpoints*

Table 30 displays mean weight and mean (absolute and percent) change in weight from baseline, and the difference in percent change from baseline in weight of ALKS 3831 versus olanzapine at each assessment visit in the 24-week double-blind period. The largest difference in mean percent weight change (-1.8%) occurred at Week 24 (Day 169)—The difference in mean weight gain was -3.0 kg = 78.93 kg ALKS 3831 - 81.93 kg olanzapine. Around two thirds of the subjects (177 on ALKS 3831 and 175 on olanzapine) completed the Week 24 weight assessment.

**Table 29: Weight and Change from Baseline in Weight by Analysis Visit—Observed Cases (Study A303)**

Analysis Visit (Days)	ALKS 3831 (N=266)				Olanzapine (N=272)				Difference in Percent Change (%)
	N	Weight (kg)	Change from Baseline in Weight (kg)	Percent Change from Baseline (%)	N	Weight (kg)	Change from Baseline in Weight (kg)	Percent Change from Baseline (%)	
8	265	77.66 (13.72)	0.67 (1.48)	0.92 (2.00)	269	78.29 (13.65)	0.90 (1.62)	1.20 (2.21)	-0.28
15	248	78.28 (13.84)	1.37 (2.05)	1.84 (2.64)	265	78.83 (13.63)	1.39 (2.16)	1.86 (2.88)	-0.02
29	236	78.82 (13.77)	2.04 (2.62)	2.77 (3.54)	249	80.10 (14.09)	2.44 (3.04)	3.23 (4.02)	-0.46
43	229	79.46 (13.76)	2.56 (3.01)	3.47 (4.17)	244	80.92 (14.31)	3.29 (3.48)	4.33 (4.62)	-0.86
57	218	78.95 (13.59)	2.58 (3.45)	3.54 (4.80)	233	81.59 (14.33)	3.45 (3.66)	4.46 (4.71)	-0.92
85	214	78.92 (13.90)	2.71 (3.98)	3.72 (5.60)	220	82.05 (14.13)	3.82 (4.22)	4.93 (5.26)	-1.21
113	199	78.98 (13.98)	3.08 (4.65)	4.26 (6.50)	202	82.24 (14.30)	4.19 (4.95)	5.44 (6.25)	-1.18
141	185	78.92 (13.90)	3.01 (5.33)	4.21 (7.41)	187	81.58 (14.09)	4.06 (5.32)	5.37 (6.78)	-1.20
169	177	78.93 (14.15)	2.80 (5.61)	3.91 (7.72)	175	81.97 (14.67)	4.37 (5.96)	5.72 (7.56)	-1.81

Abbreviations: N: the number of subjects observed at each Analysis Visit Day; SD: Standard Deviation.

Note: Three subjects discontinued the study (recorded as Discontinued in End of Study Status) but were recorded as Completed in End of Treatment Status and had Week 24 weight measurement. The weight measurements were taken not more than 3 days from their last treatment day. Therefore, this reviewer included these three subjects as completers in the efficacy analysis.

Source: FDA statistical reviewer

**First Co-Primary Endpoint: Percent Change from Baseline in Weight at Week 24**

The Applicant’s primary analysis results (Table 30) for the first co-primary endpoint were obtained with ANCOVA 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 (MI) method.

The Applicant presented the hypothesis testing results based on both the CHW test statistic (primary) and the unadjusted test statistic (supportive). Both tests led to almost identical p-values (0.003 with the CHW test vs. 0.002 with the unadjusted test).

Table 30 summarizes the estimated treatment effect (corresponding to unadjusted test statistic). The treatment effect estimate was -2.38 with a 95% CI (-3.88, -0.88) in favor of ALKS 3831. Similar findings were obtained with the CHW test statistic (not presented here).

The first co-primary endpoint met a criterion for pre-specified co-primary statistical significance. The pre-specified primary analysis showed a statistical significance for evidence of superiority of ALKS 3831 over olanzapine in percent increase in weight at Week 24. However, it is uncertain whether the observed treatment difference (-2.38) in percent weight gain from baseline is clinically relevant.

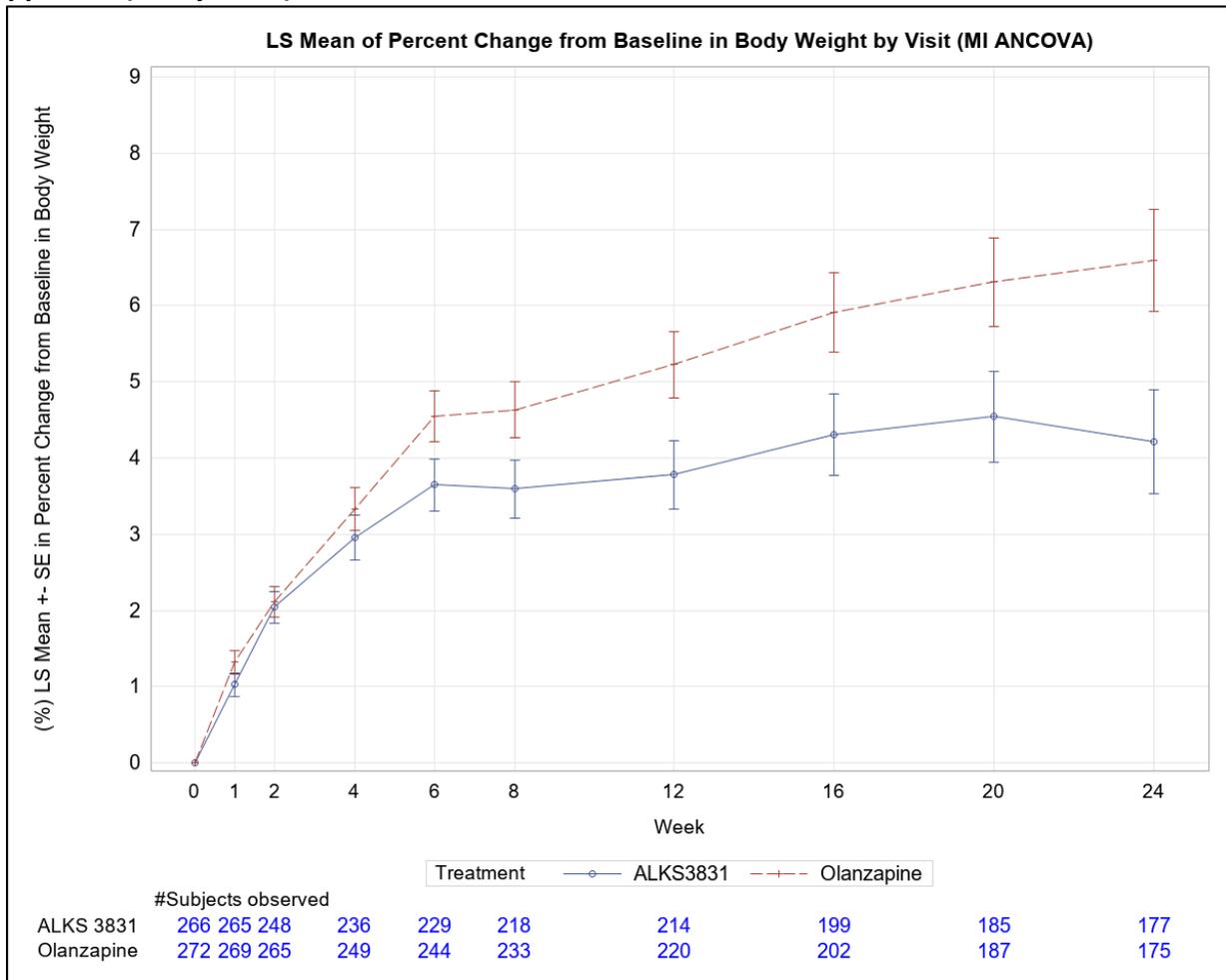
**Table 30: Primary Analysis Results for First Coprimary Endpoint (Study A303)**

Treatment group	Number of Subjects	Mean baseline weight (SD), kg	Percent Change from Baseline in Weight	
			LS mean (SE)	Treatment difference (ALKS 3831 – Olanzapine) (95% CI)
ALKS 3831	266	77.00 (13.680)	4.21 (0.681)	-2.38 (-3.88, -0.88)
Olanzapine	272	77.45 (13.478)	6.59 (0.668)	

LS: least-squares; SD: standard deviation; SE: standard error; CI: unadjusted CI.  
 Source: Table 11 of Applicant’s CSR, verified by FDA statistical reviewer

The following figure displays the percent weight gain from baseline over time. It suggests that the weight mitigation of ALKS 3831 versus olanzapine is not observed until approximately 6 weeks of treatment and then continues at a slower rate throughout the treatment period. The data do not provide information whether the apparent decline (or flattening) of mean weight gain with ALKS 3831 from Weeks 20 to 24 was caused, for example, by the impact of subjects dropping out or by an ALKS 3831 weight gain mitigation effect. Therefore, the Week 24 data should be interpreted with caution.

**Figure 16: LS Mean of Percent Change from Baseline in Body Weight by Visit (MI ANCOVA Approach) (Study A303)**



Abbreviations: MI: Multiple Imputation; ANCOVA: analysis of covariance; LS: least-squares; SE: standard error.  
 Note: The MI ANCOVA model (Primary Analysis Model) was applied on Applicant's MI data (observed and imputed data) at each visit. LS Means are based on an individual ANCOVA model for each visit, not including data from all visits in one model.  
 Source: FDA Statistical Reviewer

**Second Co-Primary Endpoint: Proportion of Subjects who had  $\geq 10\%$  Increase from Baseline in Weight at Week 24**

The Applicant's primary analysis results (Table 31) for the second co-primary endpoint was obtained with the Logistic Regression 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 (MI) method. Through logistic regression analysis, treatment effect was primarily assessed by odds ratio, but risk difference was also obtained. Similar to the first co-primary endpoint, the Applicant presented the hypothesis testing results based on both the CHW test statistic (primary) and the unadjusted test statistic (supportive). Both tests led to a p-value less than 0.01 (p=0.003 with the CHW test versus 0.004 with the unadjusted test). Table 31 summarizes the estimated treatment effects in terms of odds ratio (primary) and risk

difference (supportive) (in line with the unadjusted test statistic). Whether in terms of odds ratio or risk difference, the results were statistically significant in favor of ALKS 3831.

**Table 31: Primary Analysis Results for Second Coprimary Endpoint (Study A303)**

Treatment Group	Number of Subjects	Number of (percent) Subjects with $\geq 10\%$ Weight Increase <sup>a</sup>	Results from logistic regression model	
			Primary Measure Odds Ratio (ALKS 3831/ Olanzapine) (95% CI)	Supportive Measure Risk Difference (ALKS 3831 – Olanzapine) (95% CI)
ALKS 3831	266	47 (17.8)	0.50 (0.31, 0.80)	-13.7 (-22.8, -4.6)
Olanzapine	272	81 (29.8)		

LS: least-squares; SD: standard deviation; SE: standard error; CI: unadjusted CI.

<sup>a</sup>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.

Source: Table 14.2.3 (Study report)

**Efficacy Results—Key Secondary Endpoint: Proportion of Subjects with  $\geq 7\%$  Increase from Baseline in Weight at Week 24**

Table 32 summarizes the estimated treatment effects in terms of odds ratio (primary measure) and risk difference (supportive measure). The results were statistically significant in favor of ALKS 3831, whether in terms of odds ratio or risk difference, and was qualitatively similar to those of the second co-primary endpoint, where the weight gain cutoff was set at 10%.

**Table 32: Primary Analysis Results for Secondary Endpoint (Study A303)**

Treatment Group	Number of Subjects	Number (percent) of Subjects with $\geq 7\%$ Weight	Results from logistic regression model	
			Primary Measure Odds Ratio (ALKS 3831/ Olanzapine) (95% CI)	Supportive Measure Risk Difference Risk (ALKS 3831 – Olanzapine) (95% CI)
ALKS 3831	266	73 (27.5)	0.50* (0.33,0.76)	-15.9 (-25.3, -6.5)
Olanzapine	272	116 (42.7)		

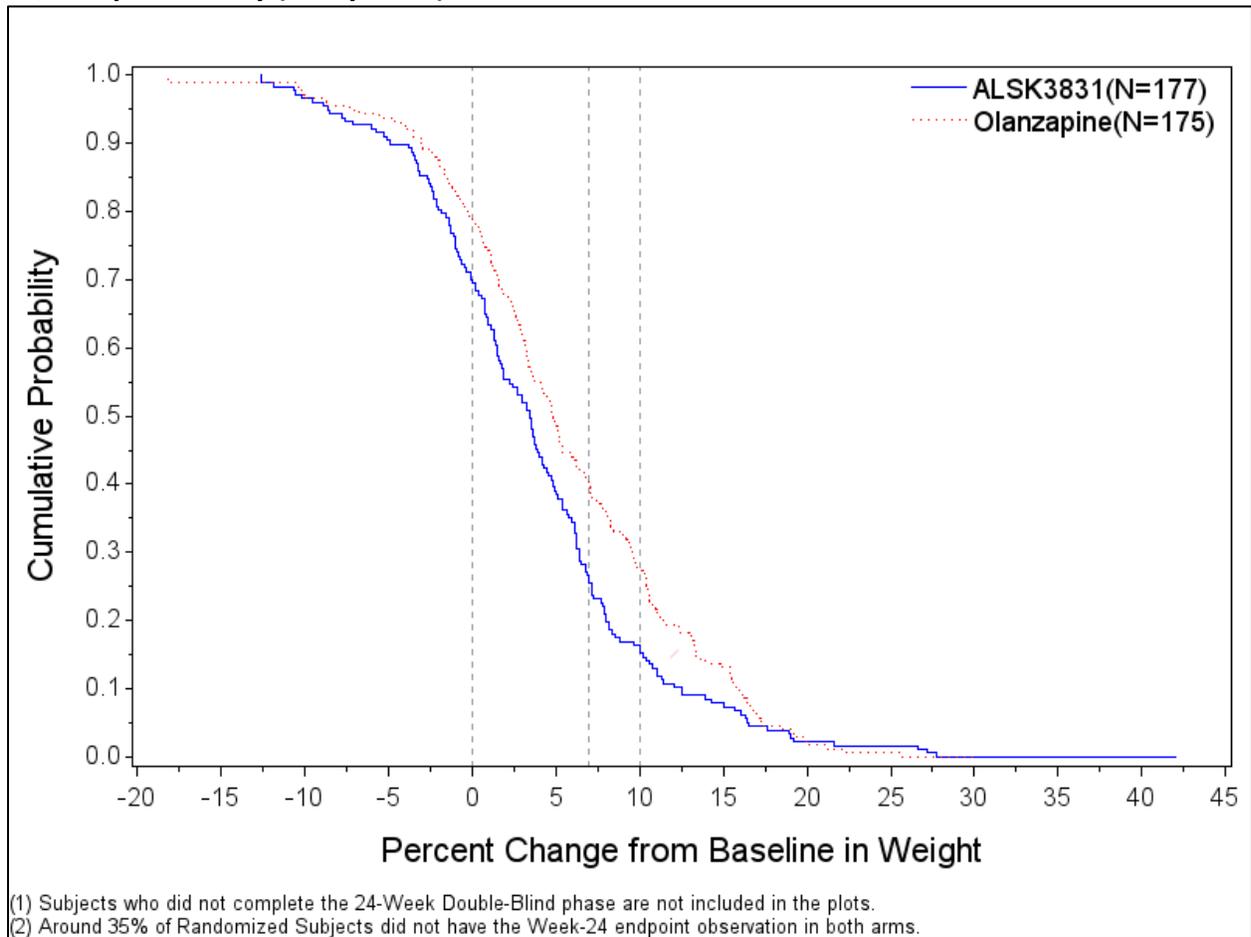
LS: least-squares; SD: standard deviation; SE: standard error; CI: unadjusted CI.

\*p-value for testing odds ratio was 0.001.

Source: Table 14.2.3, A303 Clinical Study Report

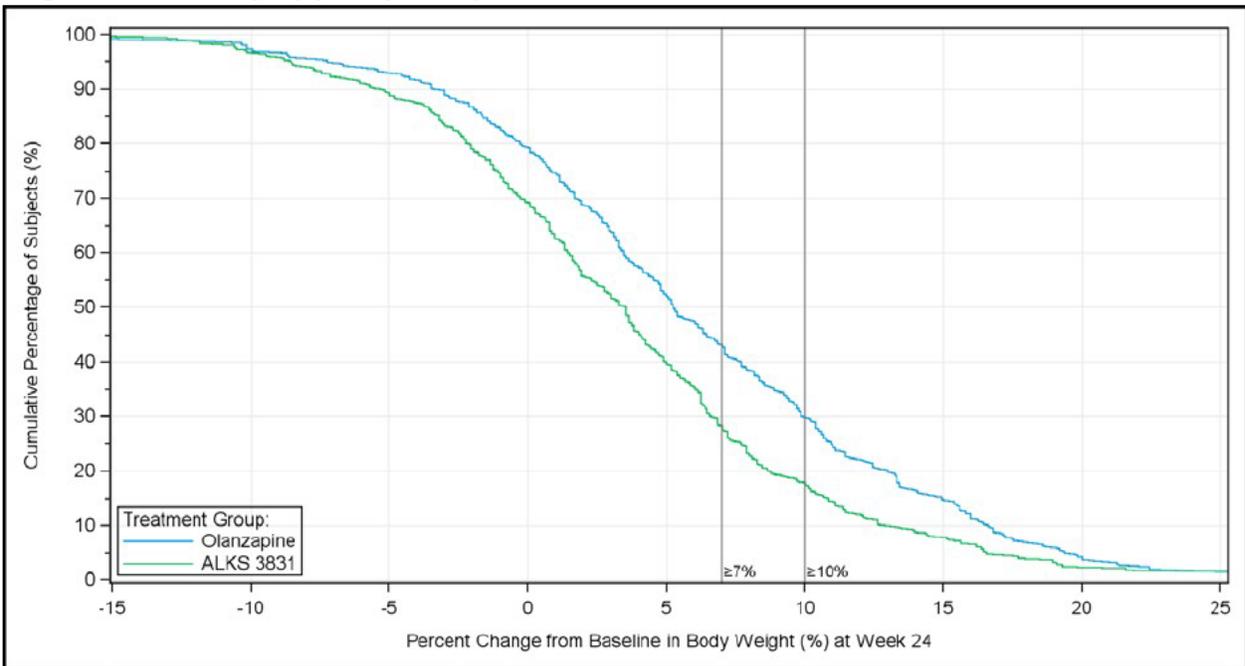
The cumulative frequency distribution plot of completers (around 65% of the randomized population) showed a left shift of the curve in the ALKS 3831 group across proportions in Week 24 weight change (). The Applicant also provided a similar plot but included imputed missing data using the MI approach.

**Figure 17: Cumulative Frequency Distribution of Percent Weight Gain from Baseline at Week 24, Completers only (Study A303)**



Source: FDA statistical reviewer

**Figure 18: Cumulative Frequency Distribution of Percent Change from Baseline in Body Weight at Week 24 (MI) (Study A303)**



Source: Applicant’s Clinical Study Report for ALK3831-A303, Figure 3, page 63

**Number-needed-to-treat**

At Week 24, the number-needed-to-treat (NNT) with ALKS 3831 to mitigate various cut-offs of weight gain with olanzapine is between six and ten patients (calculated as the inverse of the risk difference):

**Table 33: Number Needed to Treat to Mitigate Weight Gain (Study A303)**

Parameter	NNT (95% CI)
≥ 10% weight gain	7.29 (95% CI 4.38, 21.74)
≥ 7% weight gain	6.29 (95% CI 3.95, 15.43)
≥ 5% weight gain	7.85 (95% CI 4.50, 30.84)
≥ 0% weight gain	10.35 (95% CI 5.64, 63.03)

Source: A303 CSR Addendum, Tables 14.2.35.1, 14.2.35.2, 14.2.35.3, 14.2.35.4

**Premature Discontinuations and Missing Data**

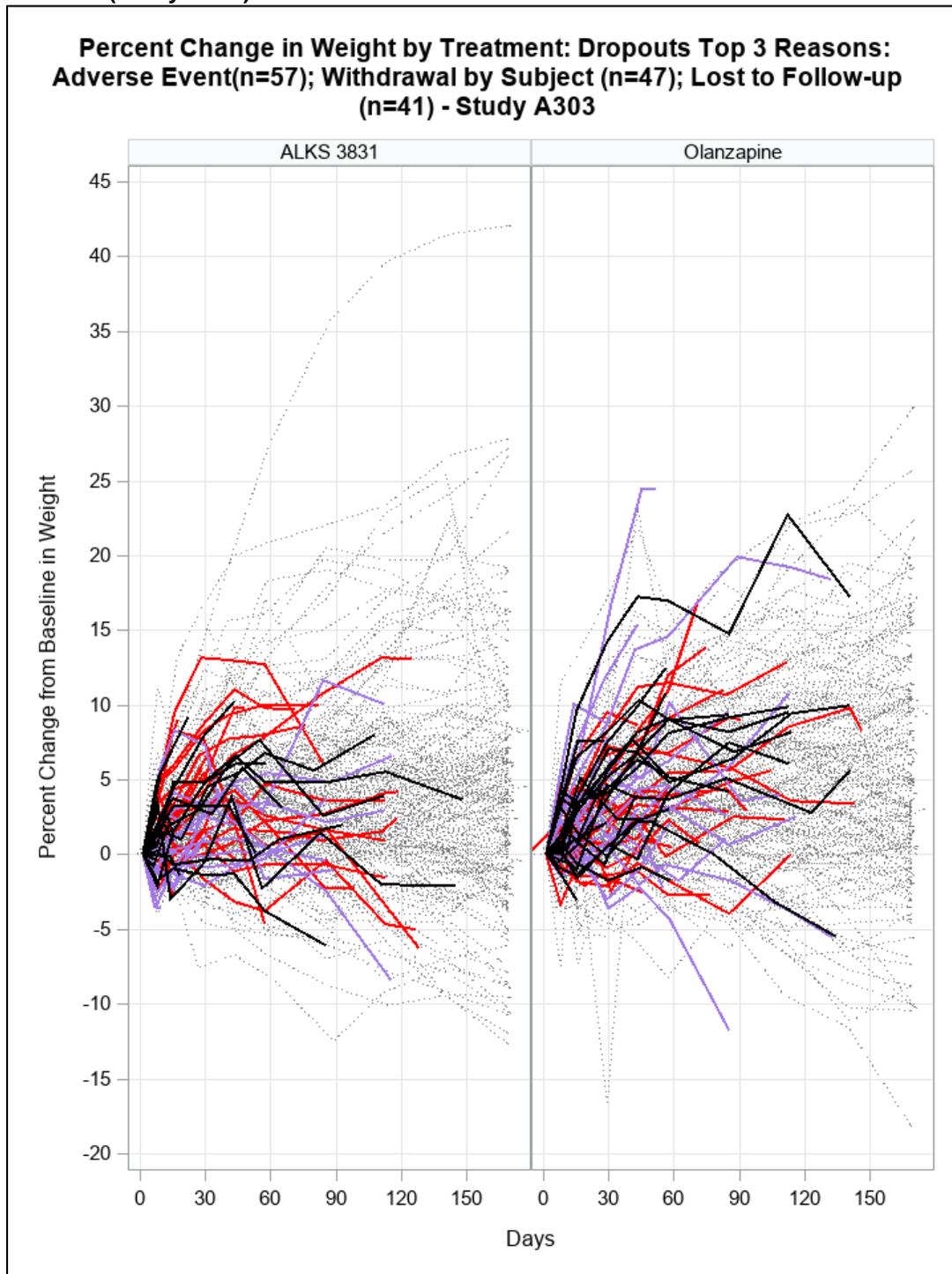
The primary multiple imputation analysis relied on the *missing at random* assumption, suggesting that all observed response trajectories can be used to impute the unobserved outcomes. Specifically, the missing data were imputed sequentially by each visit using a regression method. The imputation regression 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. In general, a weight increase was not identified as a reason for discontinuation from the assigned treatment for most of the subjects who dropped out; a relatively small proportion of subjects prematurely discontinued study drug due 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 subjects who discontinued drug in this trial reflect what will happen in practice. For example, body weight changes post-study 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.)

In this study, the top three discontinuation reasons were adverse events, withdrawal by subject, and loss to follow-up. displays the response trajectories (in terms of percent weight gain) by subjects who discontinued treatment with one of the top three dropout reasons. Completers are included as a reference and are represented by dotted gray lines. The red, purple, and black lines represent those with dropout reasons of adverse events, withdrawal by subject, and loss to follow-up, respectively. This figure suggests that in each treatment group, there was a wide range of percent weight gain at Week 24, and some completers had larger percent weight gain than most dropouts regardless of dropout reason. A few olanzapine dropouts had drastic worsening trend before dropping out, but similar trends were also observed in some olanzapine completers. More refined response trajectories separated by dropout reason are included in Appendix 17.3.1.

**Figure 19: Weight Gain Trajectories of Individual Dropouts with Top Three Discontinuation Reasons (Study A303)**



Performed on the primary efficacy analysis set.

Note: Different colors represent different discontinuation reasons: red: adverse events; purple: withdrawal by subject; black: lost to follow-up. Dotted gray lines represent completers as a reference.

Source: FDA statistical reviewer

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 pre-specified sensitivity analyses:

- The first pre-specified sensitivity analysis was based on the delta-adjusted pattern mixture model (see Table 34). 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 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  $2.38 \times 80\% = 1.9\%$ ), 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 34: Sensitivity Analysis of Percent Change from Baseline in Body Weight at Week 24 – Delta Adjusted Pattern Mixture Model – Efficacy Population (Study A303)**

	Shift Parameter	ALKS 3831
<b>Primary Analysis</b>	0	—
LS Mean Difference (SE) vs. Olanzapine	—	-2.38 (0.77)
<i>p</i> -value	—	0.002
<b>70% of Treatment Difference Between ALKS 3831 and Olanzapine (%)</b>	-1.66	—
LS Mean Difference (SE) vs. Olanzapine	—	-1.61 (0.762)
<i>P</i> -value	—	0.035
<b>80% of Treatment Difference Between ALKS 3831 and Olanzapine (%)</b>	-1.90	—
LS Mean Difference (SE) vs. Olanzapine	—	-1.51 (0.763)
<i>P</i> -value	—	0.048

	Shift Parameter	ALKS 3831
<b>90% of Treatment Difference Between ALKS 3831 and Olanzapine (%)</b>	-2.14	—
LS Mean Difference (SE) vs. Olanzapine	—	-1.41 (0.764)
P-value	—	0.066
<b>100% of Treatment Difference Between ALKS 3831 and Olanzapine (%)</b>	-2.38	—
LS Mean Difference (SE) vs. Olanzapine	—	-1.31 (0.765)
P-value	—	0.087

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error.

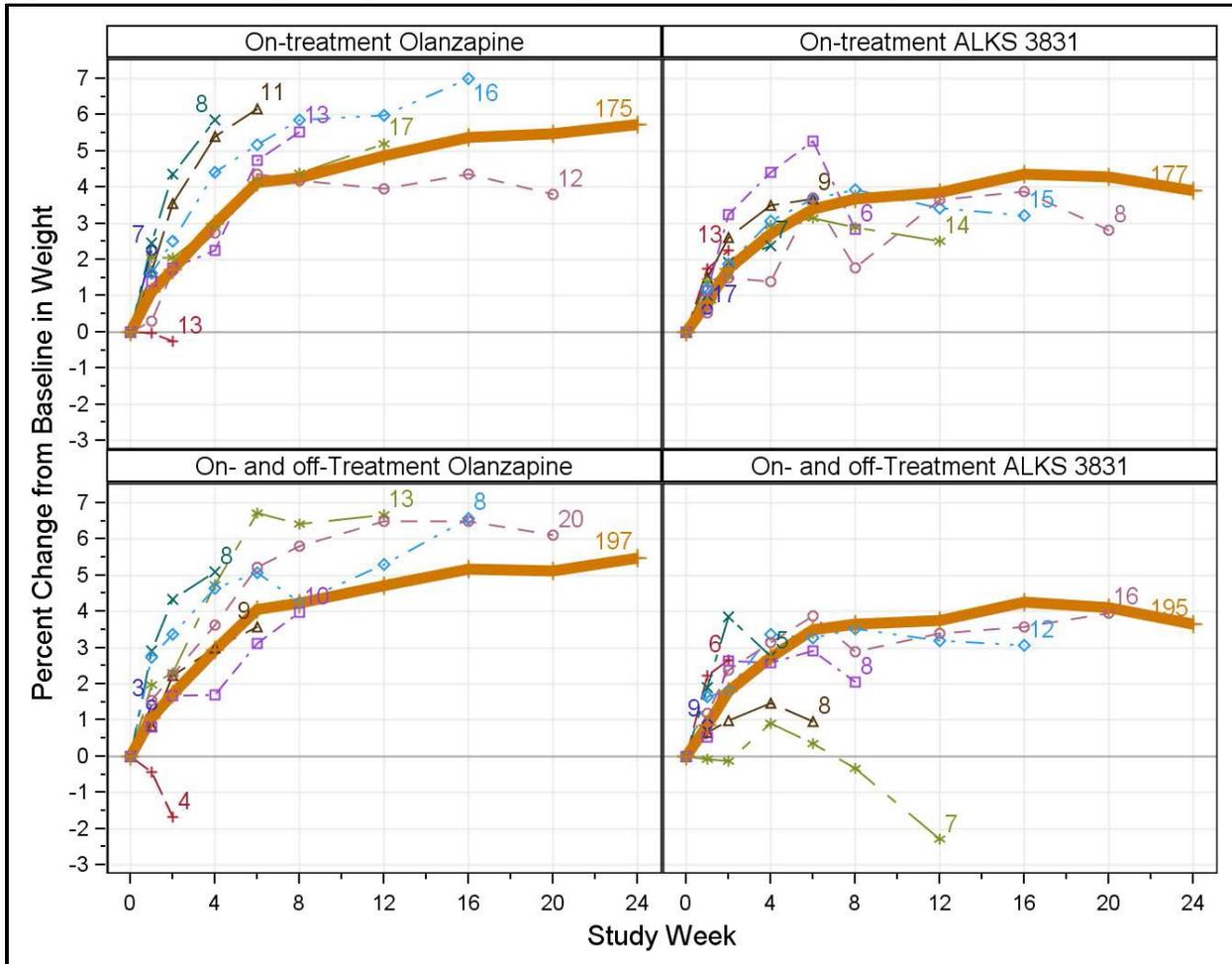
Notes: Estimates and p-values were unadjusted for the sample size increase. The delta adjusted pattern mixture model is implemented using multiple imputation with 500 imputations to incorporate the assumption of missing-not-at-random. Olanzapine subjects who discontinue would have, on average, their unobserved percent weight gain decreased by the shift parameter compared with the observed weight gain of olanzapine subjects who continue. 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. 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.

Source: extracted from Tables 11 and 13 of Applicant's CSR, confirmed by FDA statistical reviewer

- 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 20 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 30). 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 20: Mean Weight Trajectories of Subjects in Various Cohorts (Study A303)**



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

**Table 35: Sensitivity Analysis by Including both On- and Off-treatment Weight Assessments after Premature Discontinuation of Study Drug (Study A303)**

Treatment group	Sensitivity Analysis (including both on-treatment and off-treatment weight assessments)		Primary Analysis (including on-treatment weight assessments)	
	LS mean (SE)	Treatment difference (ALKS 3831 – Olanzapine) (95% CI)	LS mean (SE)	Treatment difference (ALKS 3831 – Olanzapine) (95% CI)
ALKS 3831	3.89 (0.637)	-2.40	4.21 (0.681)	-2.38
Olanzapine	6.29 (0.626)	(3.81, 1.00)	6.59 (0.668)	(-3.88, -0.88)

LS: least-squares; SD: standard deviation; SE: standard error; CI: unadjusted CI.

Source: Table 14.2.1 and Table 14.2.2.3.2 of Applicant’s CSR, confirmed by FDA statistical reviewer

- The Applicant performed a third pre-specified 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% (-3.79, -0.85).

The Applicant also performed the same sensitivity analyses on the second co-primary endpoint (proportion of subjects with  $\geq 10\%$  in weight gain at Week 24). The results support the robustness of the primary analysis on this categorical co-primary 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 co-primary endpoint (proportions of subjects with  $\geq 10\%$  in body weight from baseline to Week 24) in which subjects with missing weight assessments at Week 24 were imputed as (1) gaining  $\geq 10\%$  in body weight from Baseline at Week 24, and (2) not gaining that amount of weight ( $<10\%$ ) at Week 24. As seen in , imputing missing as  $\geq 10\%$  weight gain or less than amount results in some attenuation of the treatment effect, both measured by odds ratio and risk difference.

**Table 36: Proportion of Subjects with  $\geq 10\%$  Weight Gain from Baseline at Week 24 by Imputation Method (Study A303)**

	Imputation Method for Missing Data	ALKS 3831 N=266 n (%)	OLZ N=272 n (%)	ALKS 3831 vs. OLZ Odds Ratio (95% CI)	ALKS 3831 vs. OLZ Risk Difference (95% CI)
$\geq 10\%$ Weight Gain at Week 24	Primary Analysis (MI for missing data)	47 (17.8)	81 (29.8)	0.50 (0.31, 0.80)	-13.7 (-22.8, -4.6)
	Impute Missing as $\geq 10\%$ Weight Gain	119 (44.7)	146 (53.7)	0.69 (0.49, 0.98)	-8.9 (-17.4, -0.5)
	Impute Missing as $< 10\%$ Weight Gain	30 (11.3)	49 (18.0)	0.57 (0.35, 0.93)	-6.7 (-12.7, -0.8)

Source: Response (eCTD 0005) to Agency Request for Information dated 07 May 2020 – Part 1, Tables Q2.1 and Q2.2

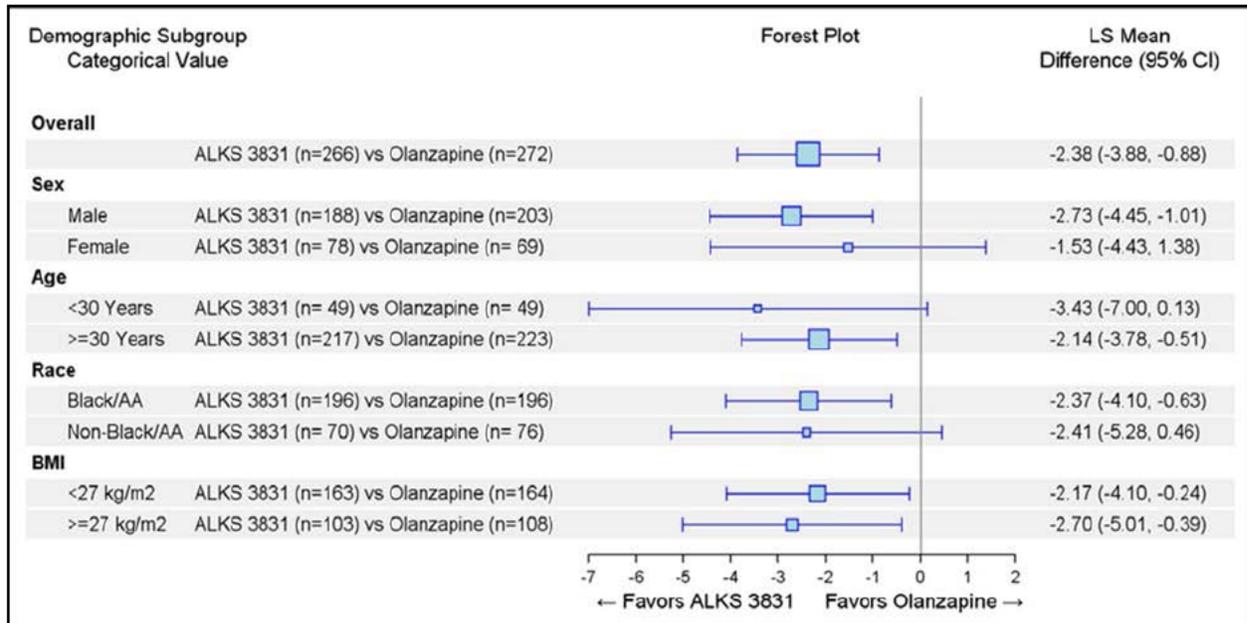
It is also possible that the olanzapine dropouts would have, on average, had much larger percent weight gains, had they not dropped out, in which case the estimated treatment effect would likely be larger than that of the primary analysis. The uncertainty lies in whether the unobserved outcomes can be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

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

#### Exploratory Subgroup Analyses

Across demographic subgroups and baseline BMI categories, the co-primary endpoint of mean percent change in body weight from baseline was consistent (). A forest plot of proportions of subjects with  $\geq 10\%$  weight gain across subgroups was generally similar (not shown here).

**Figure 21: Forest Plot of Percent Change from Baseline in Body Weight at Week 24 (Study A303)**



Abbreviations: AA=African American; ANCOVA=analysis of covariance; BMI=body mass index; CI=confidence interval; FAS=full analysis set; LS mean=least squares mean, MI=multiple imputation.  
 Source: A303 CSR, Figure 9

- The Applicant conducted exploratory weight gain analyses on an ‘early weight gain’ population, defined as those who gained any weight at Week 1. We put less emphasis on these analyses, given that weight gain at Week 1 is a post-randomization factor. They are included here for completeness.

Of the efficacy population, 177 of 272 patients on ALKS 3831 (65.1%) and 194 out of 266 patients on olanzapine (72.9%) gained any weight at Week 1.

In this subgroup of study subjects with early weight gain, mean baseline weight was 76 kg in the ALKS 3831 group and 77 kg in the olanzapine group. At Week 24, LS mean (95% CI) weight gain was 5.56% (3.96, 7.17) in the ALKS 3831 group and 7.51% (5.95, 9.07) in the olanzapine group, for a LS mean difference (ALKS 3831 – olanzapine) of -1.95% (-3.79, -0.10). The proportion of subjects in the early weight gain population with ≥ 10% weight gain from baseline at Week 24 was 40/177 (22.6%) in the ALKS 3831 group and 63/194 (32.6%) in the olanzapine group.

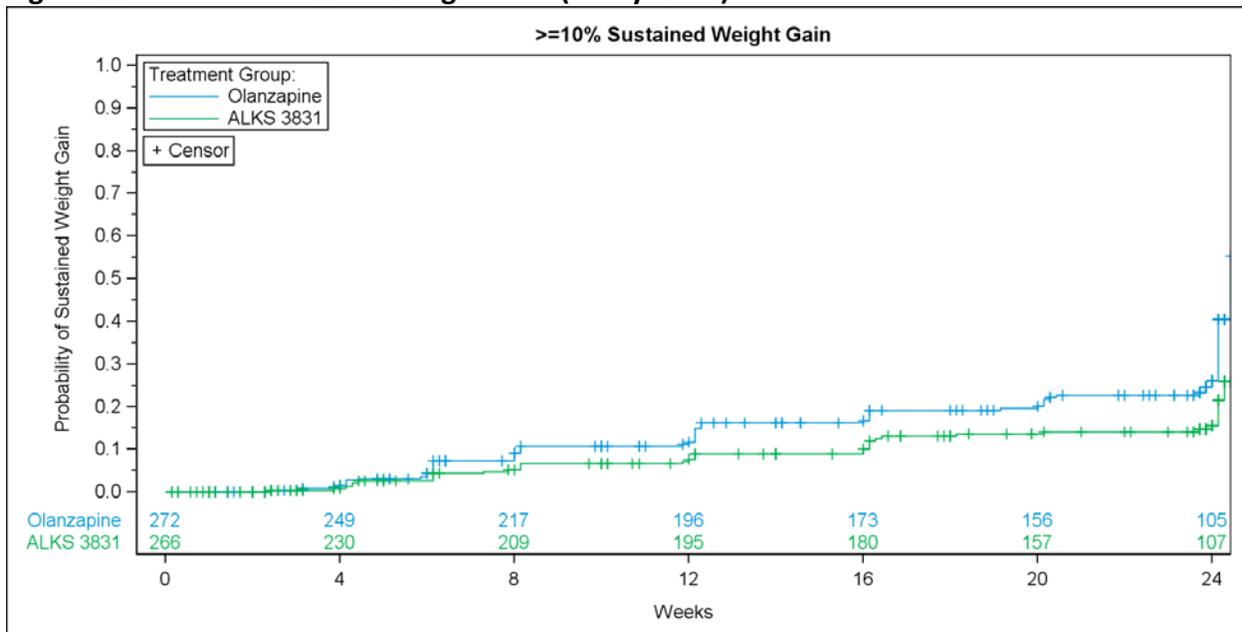
The ALKS 3831 treatment effect for weight in this subgroup is not substantially different (although numerically smaller) than that of the population overall. However, it does not necessarily reflect the effect of ALKS 3831 in subjects who have gained weight early on olanzapine, a population of interest. See further discussion of Study 302, which included a

1-week treatment lead-in with olanzapine.

- The Applicant also performed an analysis to evaluate time to “sustained weight gain” at various cut-offs; sustained weight gain defined as having weight gain at a particular cut-off for one and all subsequent visits. This exploratory analysis was conducted using weight cut-offs of  $\geq 5\%$ ,  $7\%$ , and  $10\%$  change from baseline, as well as two analysis sets:
  - Set 1: For subjects with sustained weight gain, the date of the first visit that met the sustained weight gain criteria was counted as the event date. All other subjects were censored at the date of last dose.
  - Set 2: For subjects with sustained weight gain or who discontinued due to weight or metabolic reasons, the date of the first visit that met the sustained weight gain criteria or the last dose date, whichever was earlier, was counted as the event date. All other subjects were censored at the date of last dose.

All exploratory analyses suggested that subjects in the olanzapine group were more likely to have sustained body weight gain than those in ALKS 3831. For the  $10\%$  analysis (Set 1), the number (%) of subjects with sustained weight gain overall was  $65 (23.9\%)$  in the olanzapine group and  $36 (13.5\%)$  in the ALKS 3831 group (see for a Kaplan-Meier plot). Discontinuations due to weight or other metabolic reasons were  $2.6\% (7/266)$  and  $3.7\% (10/272)$  in the ALKS 3831 and olanzapine groups, respectively, and the results for Set 2 were similar to Set 1.

**Figure 22: Time to Sustained Weight Gain (Study A303)**



Source: A303 CSR Addendum, Figure 1

Sensitivity Analysis for Weight-gain

Because the primary efficacy analysis did not include the off-treatment weights of subjects who had prematurely stopped drug, the safety endpoint of weight change as a potentially clinically significant (PCS) value, defined as those in the safety population who gained at least 7% body weight, could be considered a sensitivity analysis. In this supportive descriptive analysis, the treatment difference (~15%) is similar to that of the efficacy analysis. In the ALKS 3831 group, 94/270 subjects (34.8%) gained at least 7% of baseline body weight, compared to 136/273 subjects in the olanzapine group (49.8%).

Analyzing adverse events of the PT “weight increased,” particularly those that were serious or led to discontinuation, can highlight the clinical significance of weight gain during the trial (i.e., those events that were considered important enough to report as adverse) and could be used to support an efficacy claim if there were more events on olanzapine than ALKS 3831. Adverse events of weight increased were reported in 36.2% of olanzapine-treated subjects and 24.8% of ALKS 3831-treated subjects. One of the subjects in the olanzapine-treated group had a weight increased AE reported as severe. None of the events were considered serious. As noted previously, two subjects in the olanzapine group (0.7%) and four subjects in the ALKS 3831 group (1.5%) had an AE of weight increased that led to treatment discontinuation. See the safety review for further discussion of AEs in this trial.

*Other Metabolic Endpoints*

Endpoints of other weight-related endpoints were not controlled for Type I error but are presented here for descriptive purposes. Aside from waist circumference, for which the magnitude of the treatment difference is consistent with the mean weight change, each of the 95% confidence intervals of LS mean differences between ALKS 3831 and olanzapine in the other metabolic endpoints included zero. Therefore, the results are considered inconclusive; no meaningful difference in metabolic endpoint was observed between ALKS 3831 and olanzapine (see Table 37).

**Table 37: Other Secondary Metabolic Endpoints, Week 24 (Study A303)**

<b>Metabolic Endpoints</b>	<b>ALKS 3831 N=266</b>	<b>OLZ N=272</b>
<b>Waist circumference, cm<sup>a</sup></b>		
Mean (SD) baseline	90.75 (10.885)	90.92 (10.611)
Mean (SD) week 24	92.74 (11.259)	95.03 (11.780)
LS mean (95% CI) change	2.36 (1.26, 3.46)	4.47 (3.40, 5.54)
LS mean difference ALKS 3831 – OLZ (95% CI)	-2.12 (-3.35, -0.89)	
<b>Fasting total cholesterol, mg/dL<sup>b</sup></b>		
Baseline, n	265	270
Mean (SD) baseline	183.4 (34.74)	185.2 (37.27)
Week 24, n	162	166
LS mean (95% CI) change	0.66 (-3.400, 4.710)	2.48 (-1.500, 6.453)
LS mean difference ALKS 3831 – OLZ (95% CI)	-1.82 (-7.12, 3.48)	

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<b>Metabolic Endpoints</b>	<b>ALKS 3831 N=266</b>	<b>OLZ N=272</b>
<b>Fasting HDL cholesterol, mg/dL<sup>b</sup></b>		
Baseline, n	265	270
Mean (SD) Baseline	62.4 (22.42)	62.1 (21.02)
Week 24, n	162	166
LS mean (95% CI) change	-6.16 (-8.015, -4.313)	-5.74 (-7.562, -3.925)
LS mean difference ALKS 3831 – OLZ (95% CI)	-0.42 (-2.85, 2.01)	
<b>Fasting LDL cholesterol, mg/dL<sup>b</sup></b>		
Baseline, n	264	270
Mean (SD) baseline	109.6 (32.26)	112.7 (33.98)
Week 24, n	161	166
LS mean (95% CI) change	0.52 (-3.281, 4.316)	1.53 (-2.188, 5.257)
LS mean difference ALKS 3831 – OLZ (95% CI)	-1.02 (-6.01, 3.98)	
<b>Fasting triglycerides, mg/dL<sup>b</sup></b>		
Baseline, n	265	270
Mean (SD) baseline	114.4 (93.96)	107.1 (62.14)
Week 24, n	162	166
LS mean (95% CI) change	26.77 (15.408, 38.136)	29.36 (18.183, 40.532)
LS mean difference ALKS 3831 – OLZ (95% CI)	-2.58 (-17.59, 12.42)	
<b>Fasting glucose, mg/dL<sup>b</sup></b>		
Baseline, n	265	270
Mean (SD) baseline	90.3 (11.60)	91.4 (12.03)
Week 24, n	160	166
LS mean (95% CI) change	3.83 (1.69, 5.97)	2.34 (0.25, 4.43)
LS mean difference ALKS 3831 – OLZ (95% CI)	1.49 (-1.33, 4.30)	
<b>HbA1c, %<sup>b</sup></b>		
Baseline, n	266	272
Mean (SD) baseline	5.40 (0.377)	5.40 (0.420)
Week 24, n	173	173
LS mean (95% CI) change	0.05 (0.01, 0.09)	0.06 (0.02, 0.10)
LS mean difference ALKS 3831 – OLZ (95% CI)	-0.01 (-0.06, 0.05)	
<b>Fasting Insulin, µU/mL<sup>b</sup></b>		
Baseline, n	265	269
Mean (SD) baseline	12.65 (20.868)	12.12 (15.848)
Week 24, n	162	161
LS mean (95% CI) change	3.38 (-0.18, 6.94)	4.07 (0.51, 7.63)
LS mean difference in change from baseline	-0.68 (-5.54, 4.18)	

<sup>a</sup> analyzed with MI ANCOVA

<sup>b</sup> 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

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

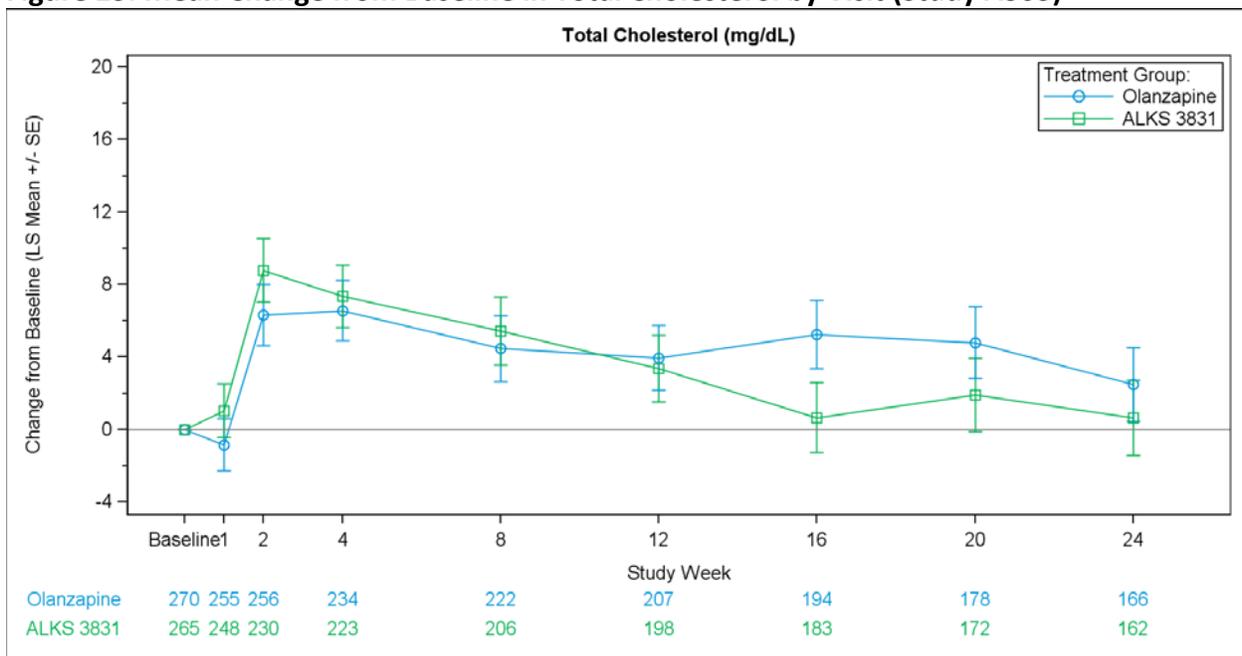
The trajectory of and proportions of subjects experiencing clinically important lipid and glycemic changes over the course of the double-blind period are discussed further below. Furthermore, given that mean changes might not fully represent the clinical impact of the

effect of ALKS 3831 on metabolic parameters, categorical changes in individual parameters are also presented.

**Lipids**

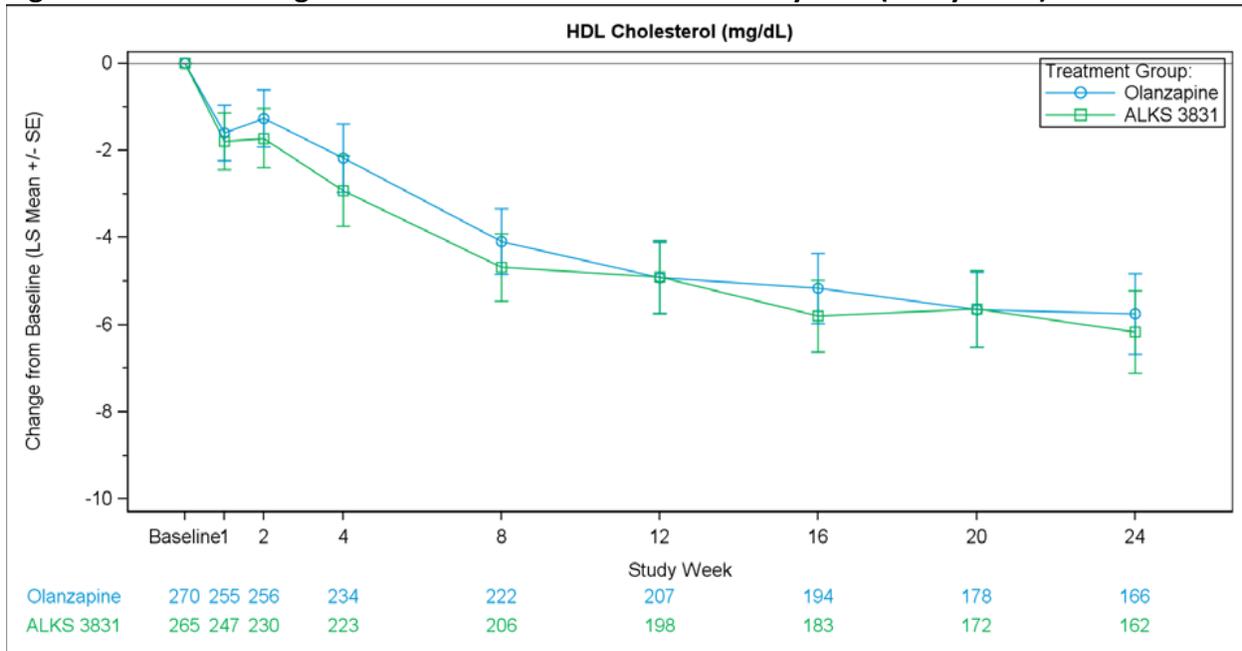
The following figure shows the trajectory of fasting lipid changes over time. In general, mean lipid changes were similar between groups, with an apparent small attenuation of the rise in total cholesterol and triglycerides (TG) with ALKS 3831 at some visits, and a small increase in LDL cholesterol (LDL-C) in the ALKS-3831 group as compared to olanzapine at Week 2 of unclear clinical significance.

**Figure 23: Mean Change from Baseline in Total Cholesterol by Visit (Study A303)**



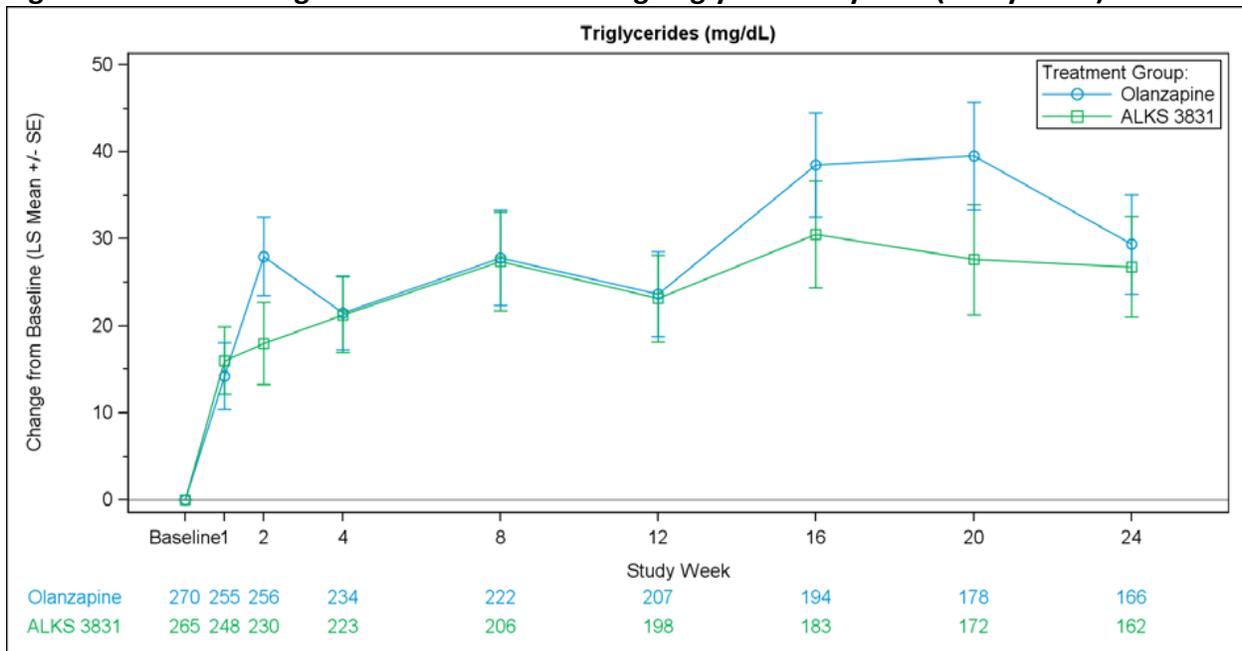
Source: A303 CSR, Figure 14

**Figure 24: Mean Change from Baseline in HDL Cholesterol by Visit (Study A303)**



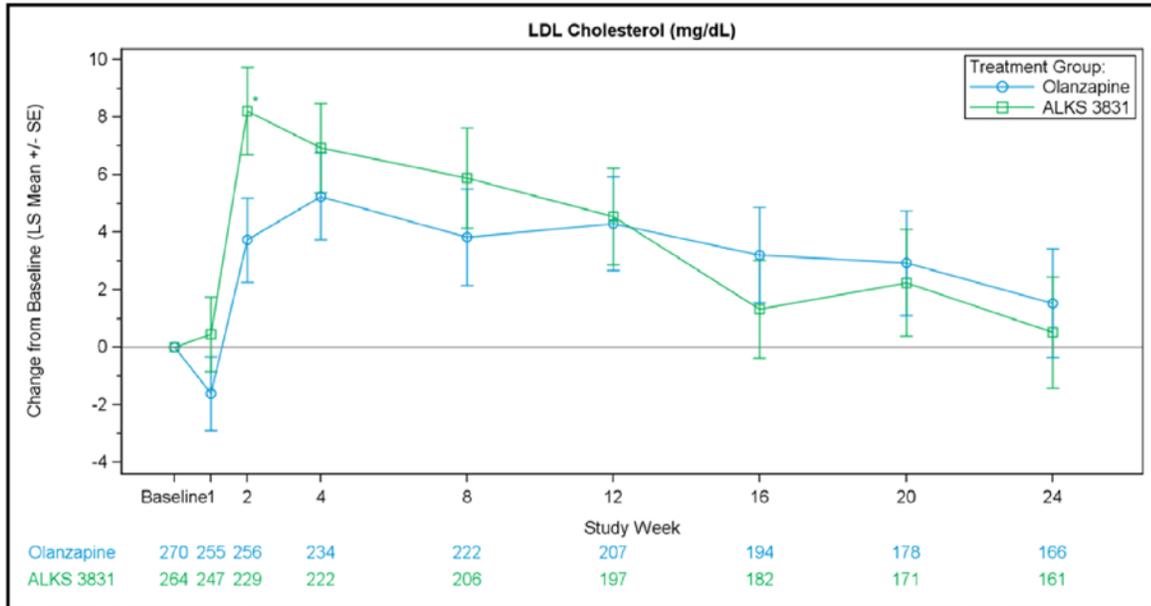
Source: A303 CSR, Figure 15

**Figure 25: Mean Change from Baseline in Fasting Triglycerides by Visit (Study A303)**



Source: A303 CSR, Figure 17

**Figure 26: Change from Baseline in LDL-C by Visit (Study A303)**



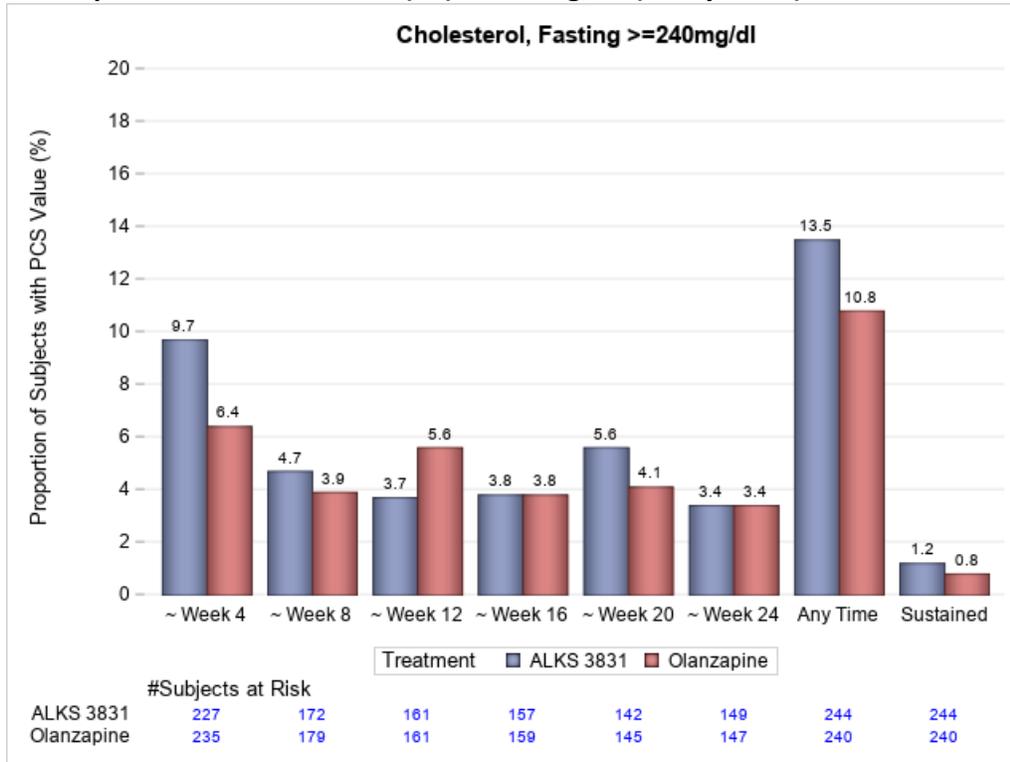
Abbreviations: LDL=low-density lipoprotein; LS=least squares; MMRM=mixed model with repeated measurements; SE=standard error.

\*P < 0.05 vs olanzapine.

Source: A303 CSR, Figure 16

In an evaluation of safety, the proportions of subjects with increases in lipid parameters tended to favor ALKS 3831 over olanzapine for triglycerides and HDL-C for most visit weeks, although “sustained” increases in lipid parameters (two on-treatment visits) were infrequent and inconsistent.

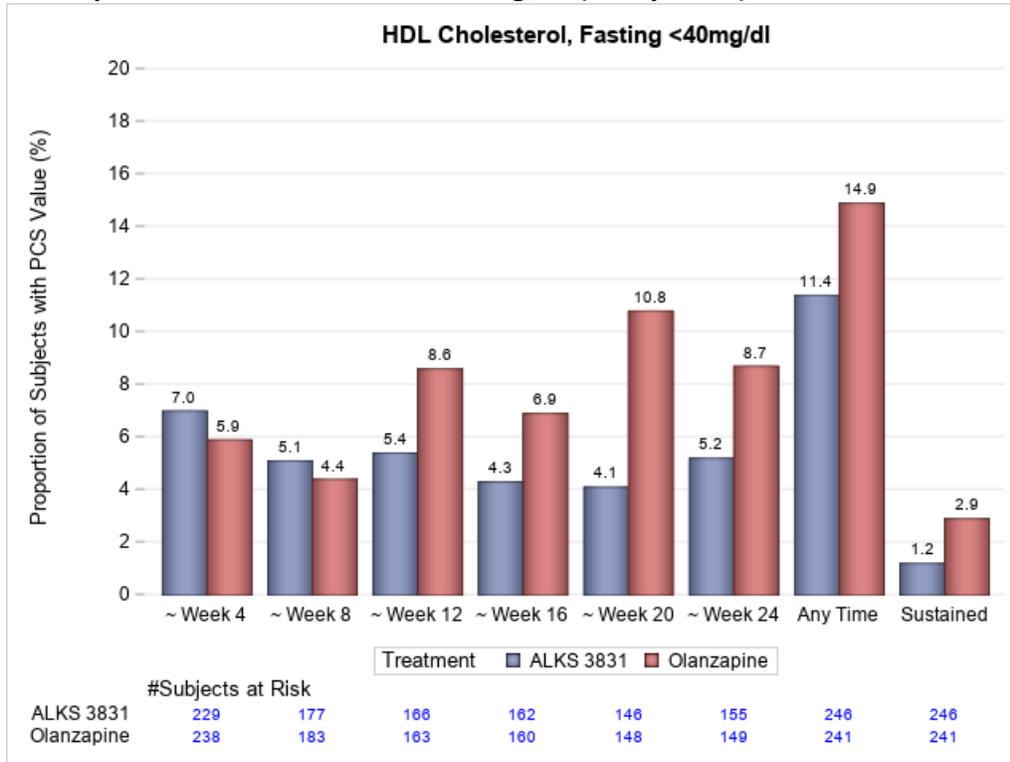
**Figure 27: Proportion of Subjects with a Baseline Total Cholesterol < 240 mg/dL and a Subsequent Total Cholesterol (TC) ≥ 240 mg/dL (Study A303)**



PCS = Potentially clinically significant; “Sustained” = subjects with two consecutive PCS outcomes at the last two visits culminating in Week 24.

Source: FDA Statistical Reviewer

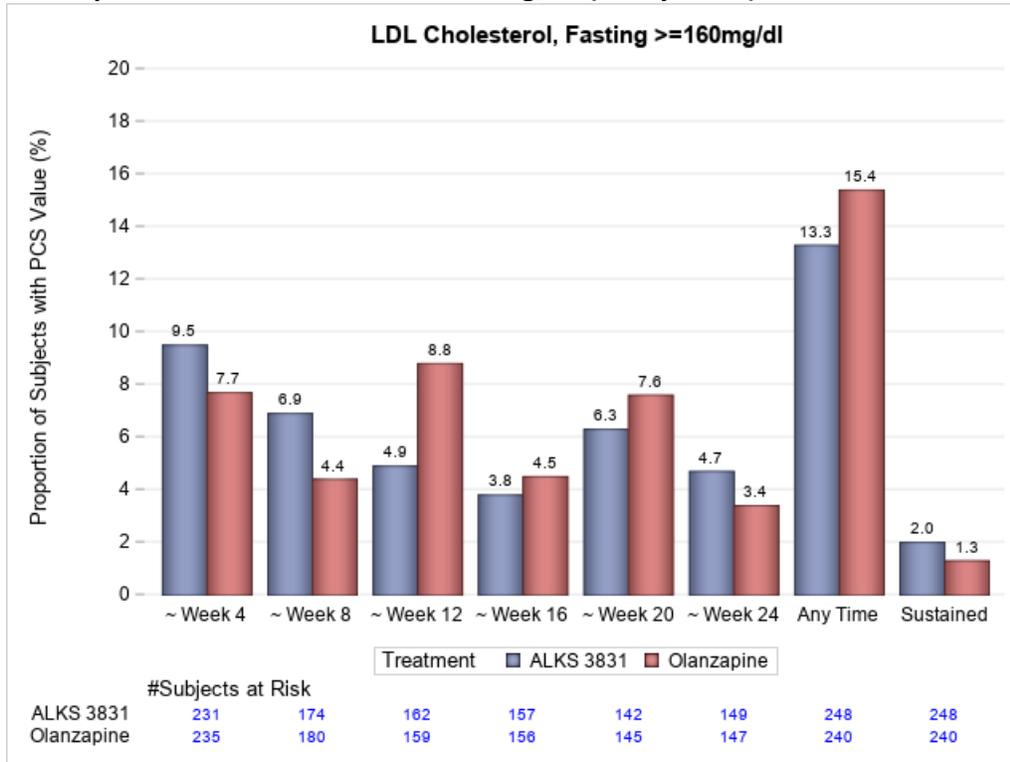
**Figure 28: Proportion of Subjects with a Baseline HDL Cholesterol of  $\geq 40$  mg/dL and a Subsequent HDL Cholesterol of  $< 40$  mg/dL (Study A303)**



PCS = Potentially clinically significant; “Sustained” = subjects with two consecutive PCS outcomes at the last two visits culminating in Week 24.

Source: FDA Statistical Reviewer

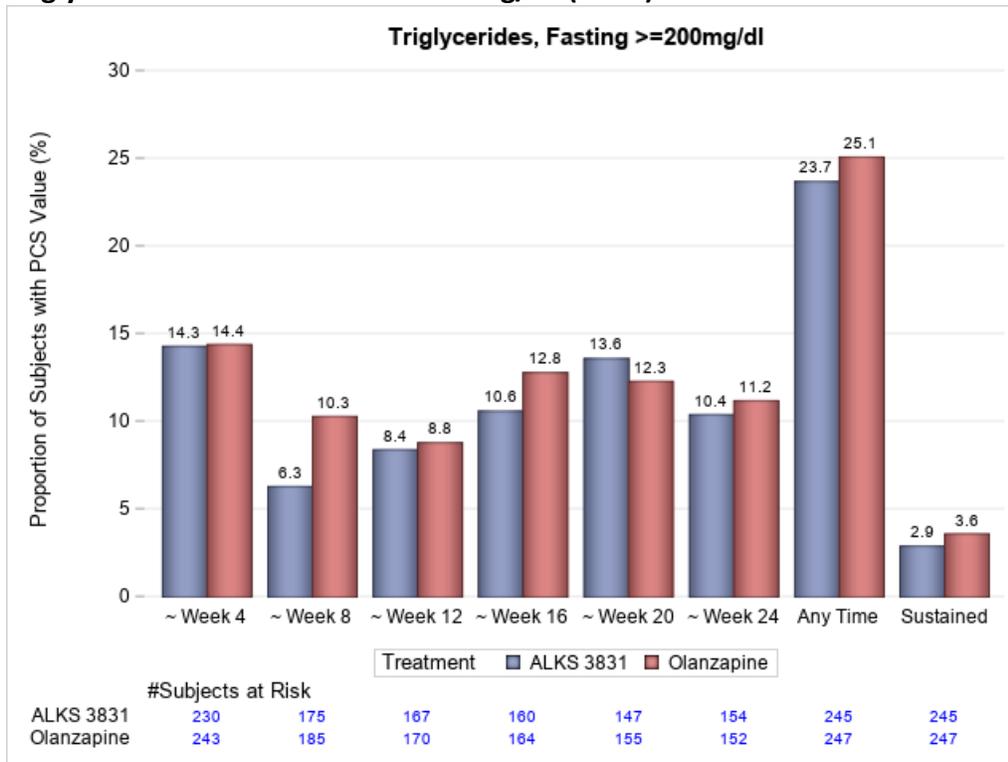
**Figure 29: Proportion of Subjects with a Baseline LDL Cholesterol of < 160 mg/dL and a Subsequent LDL Cholesterol of ≥ 160 mg/dL (Study A303)**



PCS = Potentially clinically significant; “Sustained” = subjects with two consecutive PCS outcomes at the last two visits culminating in Week 24.

Source: FDA Statistical Reviewer

**Figure 30: Proportion of Subjects with Baseline Triglycerides <200 and a Subsequent Triglyceride Measurement of ≥ 200 mg/dL (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

AEs during the treatment period from abnormal lipid profile results were similar between the treatment groups as follows: five subjects (2%) in the ALKS 3831 treatment group compared to eleven (4%) in the olanzapine group. None of these subjects discontinued the study drug.

### Glycemic Parameters

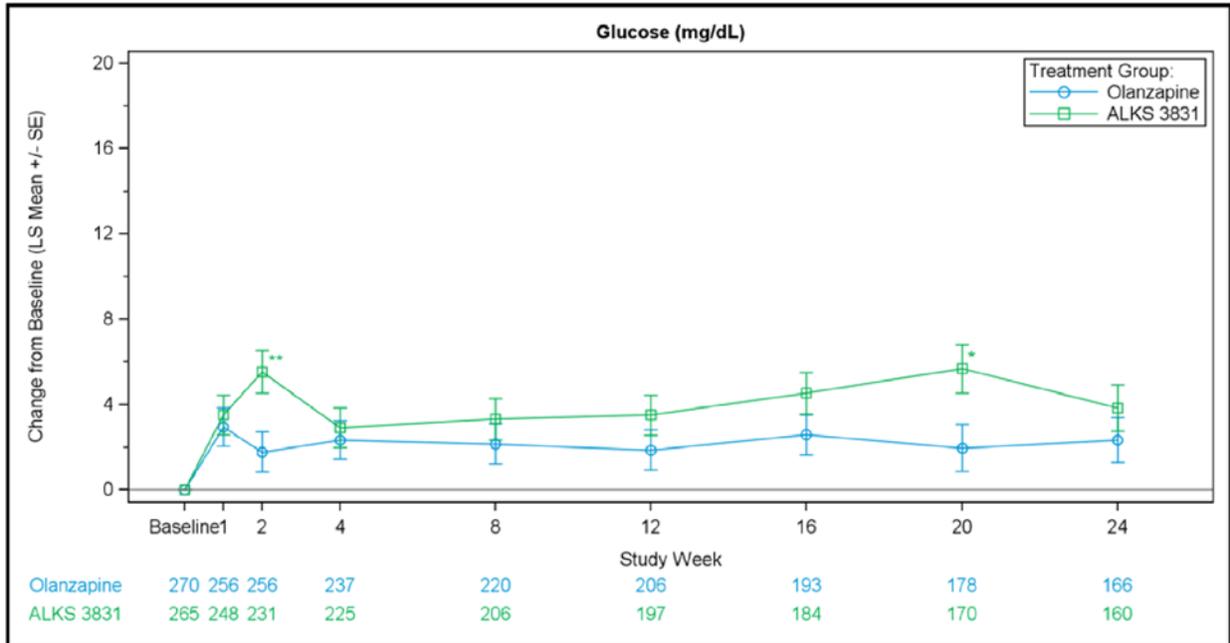
In subjects treated with ALKS 3831, there was a trend of increased fasting glucose as compared to olanzapine (see figures below). Conversely, there was a decrease in HbA1c vs. olanzapine at Week 20 (), but no difference at other timepoints. There were no differences in fasting insulin between groups (). Fasting insulin can be considered a proxy for insulin resistance in patients without diabetes mellitus, as fasting insulin rises as patients become more insulin resistant.<sup>22</sup>

The clinical significance of the observed changes in fasting glucose is unclear in a population without diabetes mellitus, where the intent of the drug is to mitigate adverse alterations in

<sup>22</sup> Quon MJ. Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. J Clin Endocrinol Metabol (2001). 86(10): 4615-7.

metabolic parameters in patients treated with olanzapine.

**Figure 31: Change from Baseline in Fasting Glucose by Visit (Study A303)**



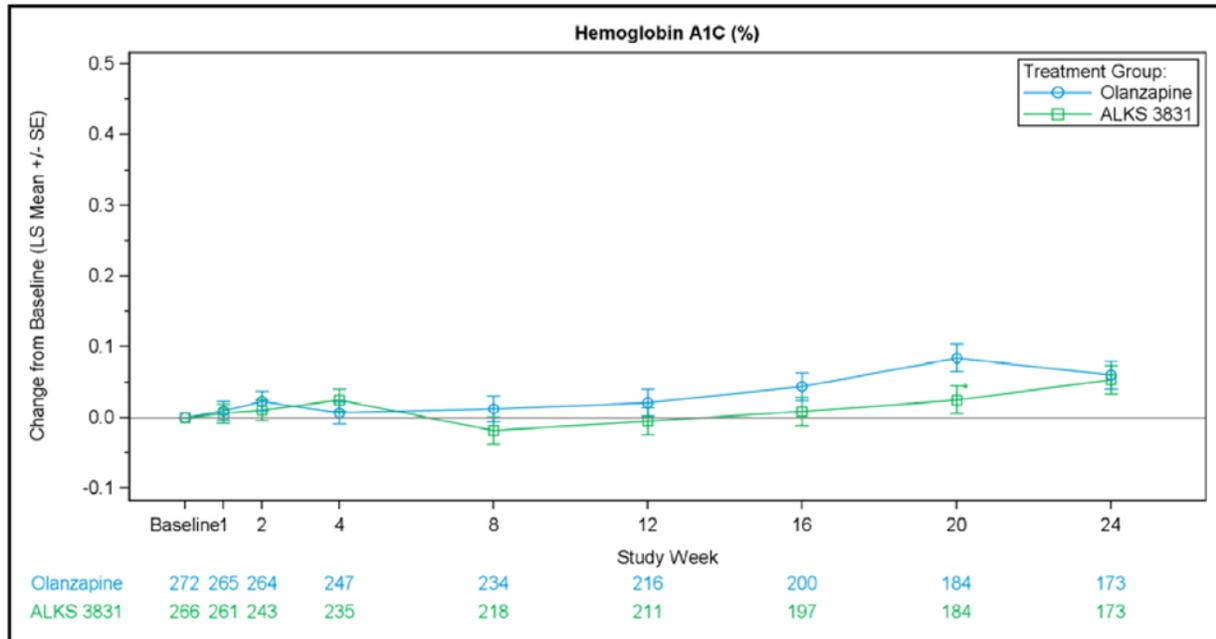
Abbreviations: LS=least squares; MMRM=mixed model with repeated measurements; SE=standard error.

\*\* $P < 0.01$  vs olanzapine; \* $P < 0.05$  vs olanzapine.

Note: The numbers in the bottom rows indicate the numbers of subjects with assessment at each visit.

Source: A303 CSR, Figure 19

**Figure 32: Change from Baseline in HbA1c by Visit (Study A303)**

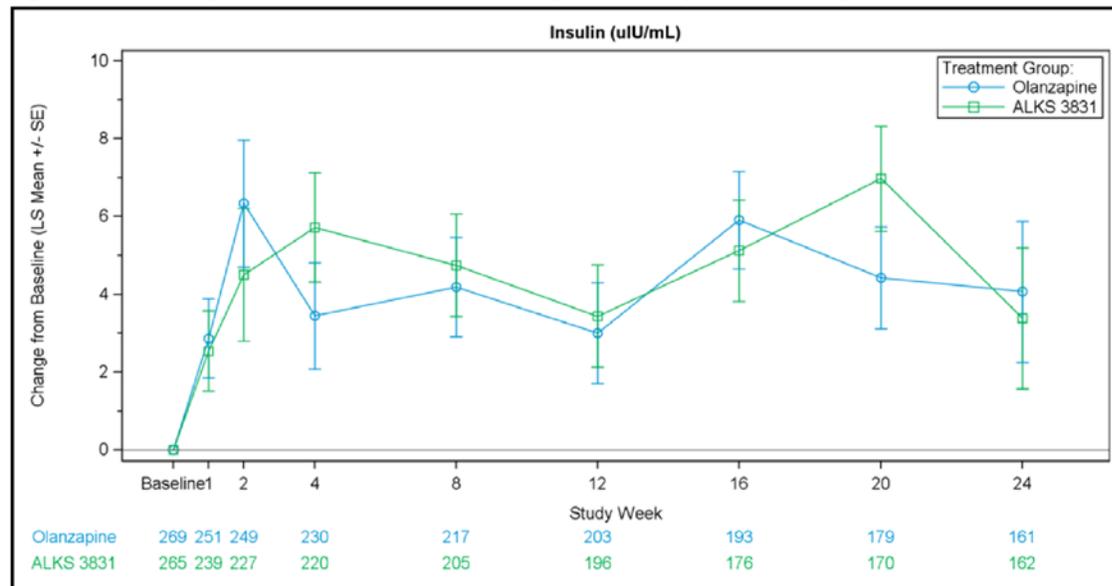


Abbreviations: LS=least squares; MMRM=mixed model with repeated measurements; SE=standard error.  
 \* $P < 0.05$  vs olanzapine.

Note: The numbers in the bottom rows indicate the numbers of subjects with assessment at each visit.

Source: A303 CSR, Figure 20

**Figure 33: Change from Baseline in Fasting Insulin by Visit (Study A303)**



Abbreviations: LS=least squares; MMRM=mixed model with repeated measurements; SE=standard error.

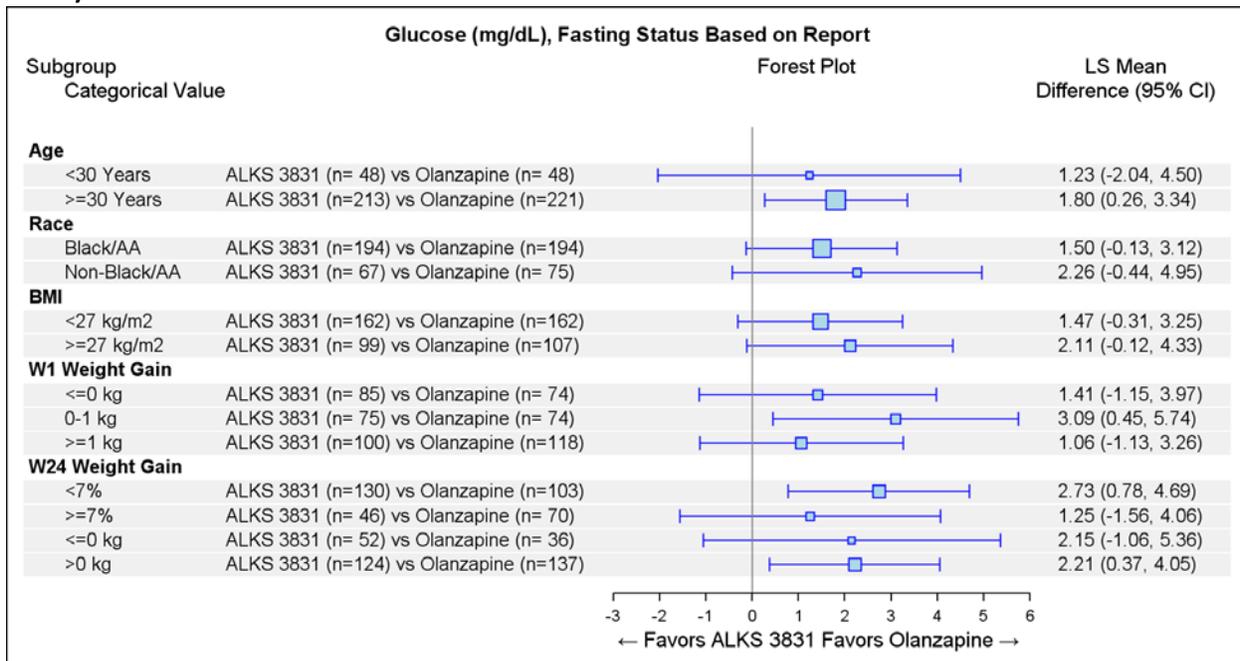
Note: The numbers in the bottom rows indicate the numbers of subjects with assessment at each visit.

Source: A303 CSR, Figure 21

Consistent with the above findings, an analysis of the time-normalized AUC of the change from baseline in glycemic parameters showed an increase in ALKS 3831 vs. olanzapine in glucose [LSM difference +1.7 mg/dL (95% CI +0.3, +3.1)] with no significant differences in insulin or HbA1c. Similar results were seen when the analysis accounted for fasting status based on report and insulin level. The Applicant conducted these exploratory analyses “to better understand the patterns of average changes over the entire course of treatment, and the differences between treatment groups, while minimizing the influence of random visit-to-visit fluctuations.”

To some extent, the increase in glucose AUC observed with ALKS 3831 appears independent of its effect on Week 24 weight gain as seen in the following figure; although, notably, the weight gain subgroups are post-randomization and therefore subject to bias.

**Figure 34: Normalized AUC of Change from Baseline in Fasting Glucose by Subgroups (Study A303)**



Source: A303 CSR Addendum, Figure 3

Separately, an evaluation of exploratory subgroup analyses of fasting glucose and insulin as change from baseline at Week 24 was conducted by the Applicant. An unfavorable trend for ALKS 3831 was seen in patients with higher BMI ( $\geq 25$  vs.  $< 25$  and  $\geq 27$  vs.  $< 27$  kg/m<sup>2</sup>) and older patients ( $\geq 30$  vs.  $< 30$  years old). No notable differences were seen in subgroups for change in HbA1c.

Several data streams from this trial were used to put these findings into clinical context, including the following safety analyses: proportions of patients with clinically significant glucose

and HbA1c outliers and shifts, additional metabolic testing, adverse events related to glycemia and diabetes mellitus, and concomitant medications for treatment of diabetes. As shown below, shifts in glycemia generally favored olanzapine (worse with ALKS 3831), but shifts in parameters of insulin resistance did not consistently favor either treatment.

**Table 38: Categorical Increases in Glucose and HbA1c (Study A303)**

	ALKS 3831 N=274	Olanzapine N=276
<b>Glucose, fasting</b>		
≥ 126 mg/dL	35/261 (13.4)	23/266 (8.6)
<b>Shifts</b>		
<b>Serum glucose (fasting) mg/dL</b>		
Normal (<100) to High (≥126)	26/223 (11.7)	18/219 (8.2)
Impaired (≥100-<126) to High (≥126)	9/38 (23.7)	5/47 (10.6)
Normal/Impaired (<126) to High (≥126)	35/261 (13.4)	23/266 (8.6)
Increase ≥ 10 mg/dL	174/265 (65.7)	154/270 (57.0)
<b>HbA1c %</b>		
Normal (< 5.7%) to Impaired/High (≥ 5.7%)	87/204 (42.6)	71/197 (36.0)
Normal (< 5.7%) to Impaired (≥5.7- <6.5%)	86/204 (42.2)	68/197 (34.5)
Normal (< 5.7%) to High (≥ 6.5%)	1/204 (0.5)	3/197 (1.5)
Impaired (≥5.7- <6.5%) to High (≥6.5%)	6/63 (9.5)	7/76 (9.2)

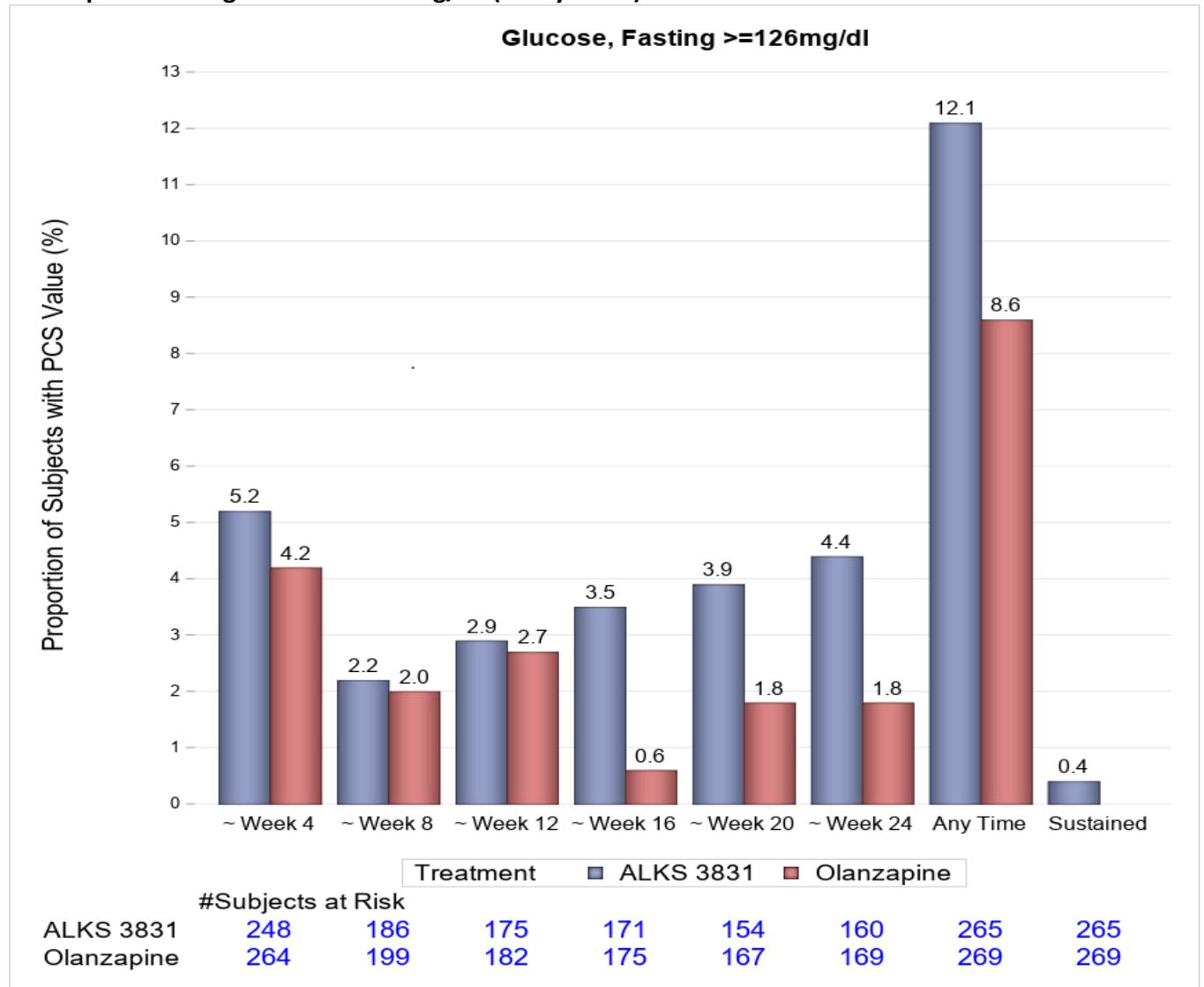
Source: A303 Table 14.3.4.3.3 and FDA clinical reviewer using ADMPCS dataset (impaired to high HbA1c)

There is an indication of small, unfavorable changes in fasting glucose with ALKS 3831 versus olanzapine. There is also a small, unfavorable imbalance in HbA1c at 5.7% or more at any visit. These findings are of unclear significance, particularly as there were few subjects in either group with sustained increases in glucose. Furthermore, the numbers of subjects with any postbaseline HbA1c ≥ 6.5% (one criterion that can be used for the diagnosis of diabetes mellitus<sup>23</sup>) were very few.

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<sup>23</sup> American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010;33(Suppl 1):S62-9.

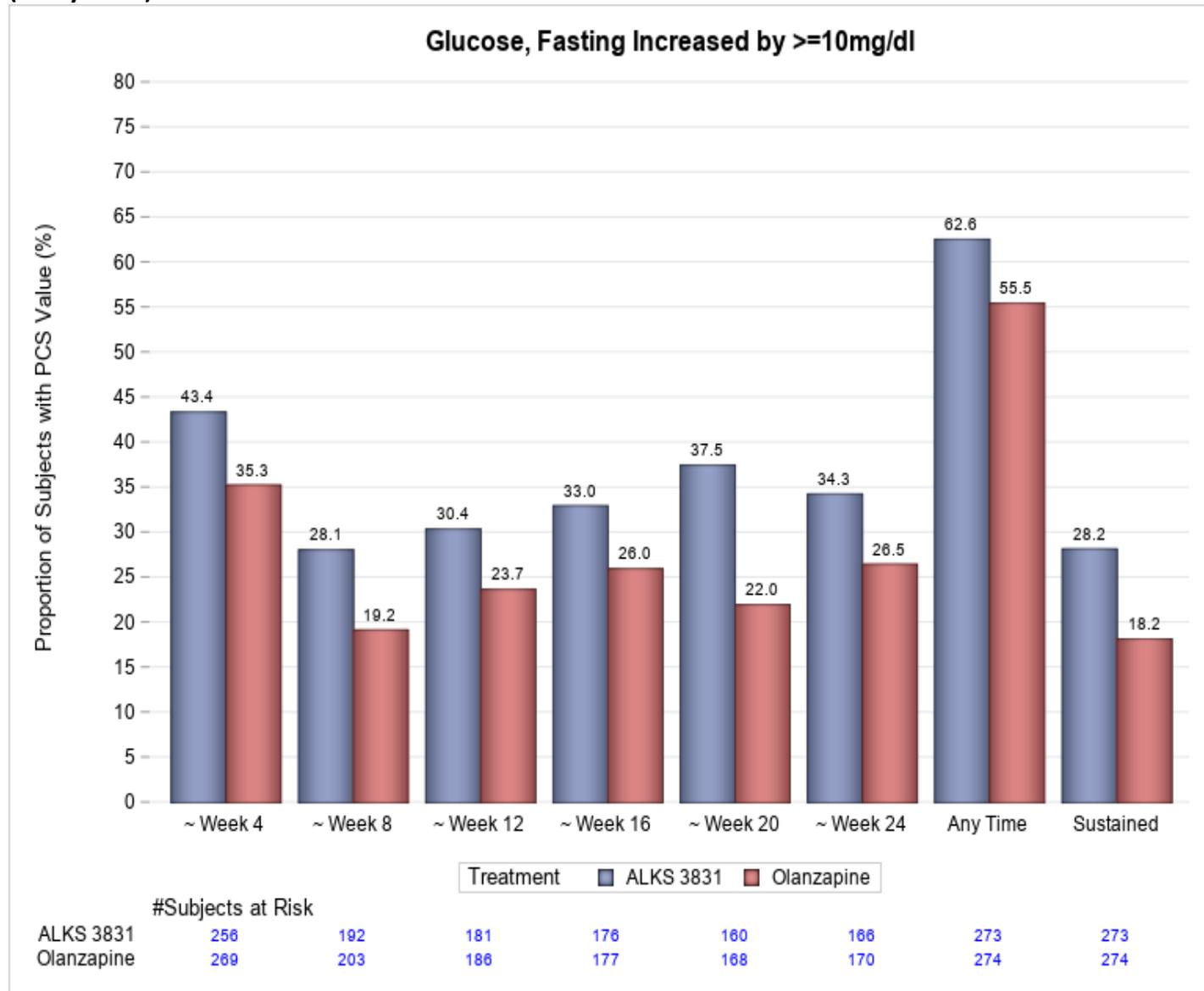
**Figure 35: Proportion of Subjects with Baseline Fasting Glucose < 126 mg/dL and a Subsequent Fasting Glucose ≥ 126 mg/dL (Study A303)**



PCS = Potentially clinically significant; “Sustained” = subjects with two consecutive PCS outcomes at the last two visits culminating in Week 24.

Source: FDA Statistical Reviewer

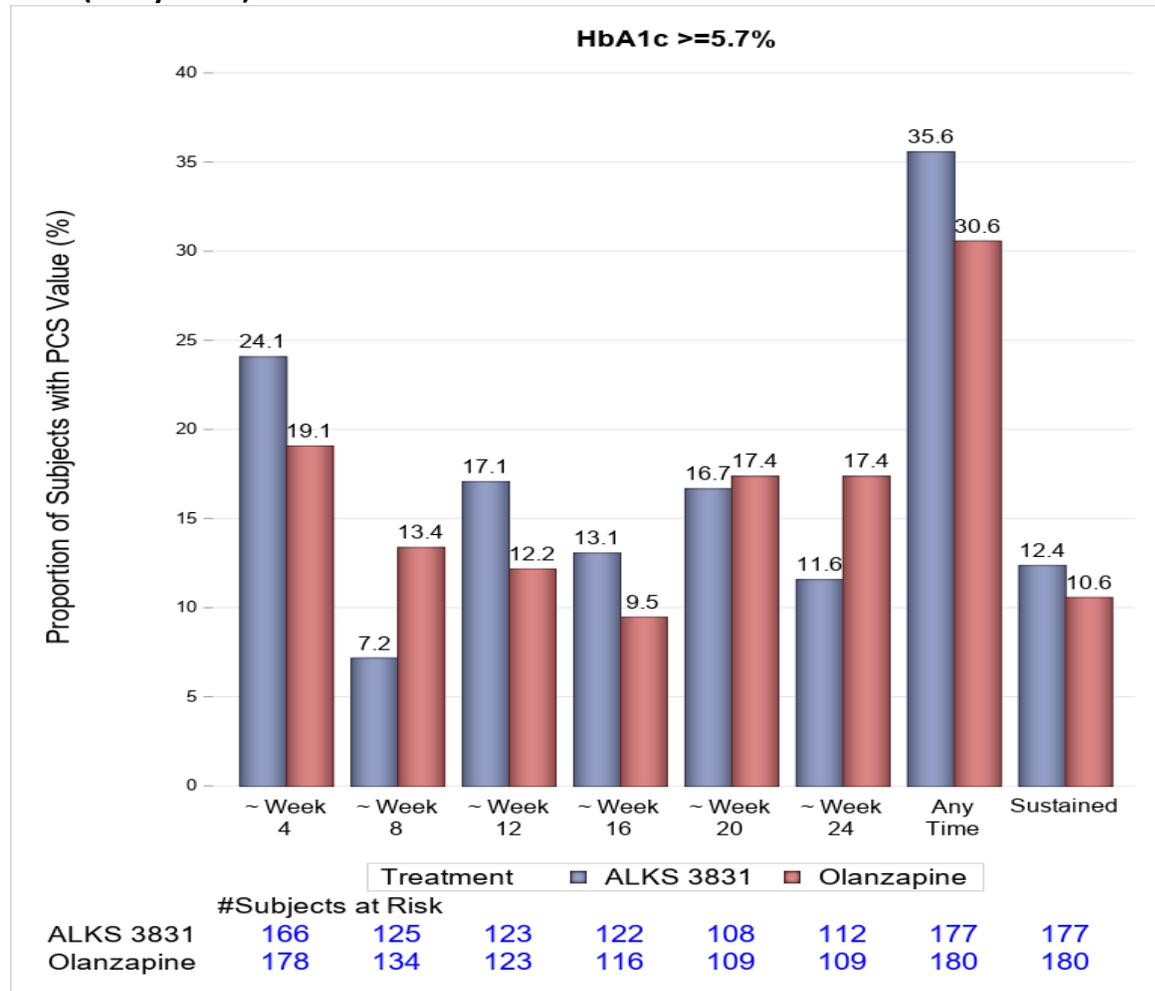
**Figure 36: Proportion of Subjects with Fasting Glucose Increase from Baseline of  $\geq 10$  mg/dL (Study A303)**



PCS = Potentially clinically significant; "Sustained" = subjects with two consecutive PCS outcomes at the last two visits culminating in Week 24.

Source: FDA Statistical Reviewer

**Figure 37: Proportion of Subjects with HbA1c < 5.7% at Baseline and a Subsequent HbA1c ≥ 5.7% (Study A303)**



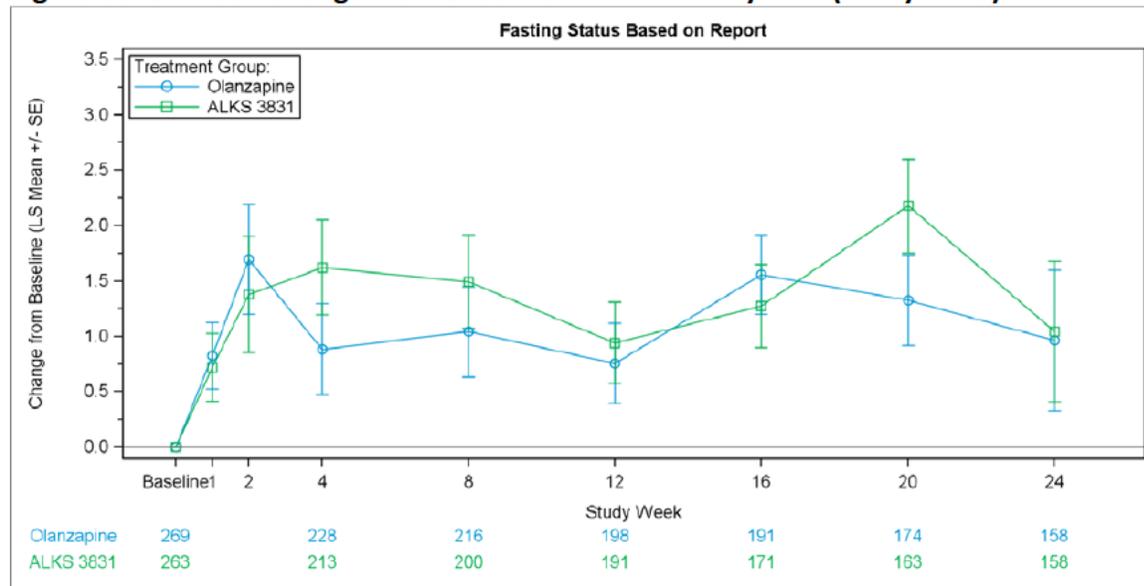
PCS = Potentially clinically significant; “Sustained” = subjects with two consecutive PCS outcomes at the last two visits culminating in Week 24.

Source: FDA Statistical Reviewer

In the analysis of fasting glucose-to-insulin ratio (lower values correlate with more insulin resistance), the mean ± SD change from baseline to Week 24 was 0.16 ± 10.438 in the ALKS 3831 group and -2.69 ± 9.363 in the olanzapine group (suggesting more insulin resistance with olanzapine).

However, in HOMA-IR, mean ± SD changes from baseline to Week 24 were ALKS 3831, 1.24 ± 10.403 and olanzapine, 0.90 ± 4.588. HOMA-IR change by visit is shown in the figure below.

**Figure 38: LS Mean Change from Baseline in HOMA-IR by Visit (Study A303)**



Source: A303 CSR Addendum, Figure 6

Finally, adverse events related to dysregulated glucose metabolism were numerically greater in the olanzapine group versus the ALKS 3831 group, with the imbalance spread across a number of preferred terms ( ).

**Table 39: Treatment-Emergent Adverse Events Related to Dysglycemia, Safety Population (Study A303)**

	ALKS 3831 N=274	Olanzapine N=276
Patients with dysglycemia-related AEs	12 (4.4)	23 (8.3)
Blood insulin increased	6 (2.2)	10 (3.6)
Glycosylated hemoglobin increased	4 (1.5)	9 (3.3)
Blood glucose increased	3 (1.1)	1 (0.4)
Hyperglycemia	1 (0.4)	0
Hyperinsulinemia	0	2 (0.7)
Diabetes mellitus	0	1 (0.4)
Glucose urine present	0	1 (0.4)

Source: Reviewer created from A303 ADAE dataset; confirmed with Table 14.3.1.2.1

Twelve of these subjects discontinued the study drug, most in the olanzapine treatment group: three in the ALKS 3831 group secondary to increased HbA1c and nine total in the olanzapine group secondary to increased HbA1c, glucose, and insulin.

One subject in each group was administered a diabetes drug (metformin) for an AE: Subject (b) (6) (olanzapine) for elevated HbA1c and Subject (b) (6) (ALKS 3831) for elevated insulin (both were recorded after study drug was discontinued but during the monthly safety

follow-up visits).

In summary, the glucose and insulin indices and related adverse events were mixed in this trial. While there is no obvious mitigation with samidorphan of the effect of olanzapine on fasting glucose, it is unclear what the impact of weight mitigation on glycemic parameters would be long-term.

#### Blood Pressure

Vital signs were collected as safety endpoints, but changes in blood pressure (BP) in particular 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 ().

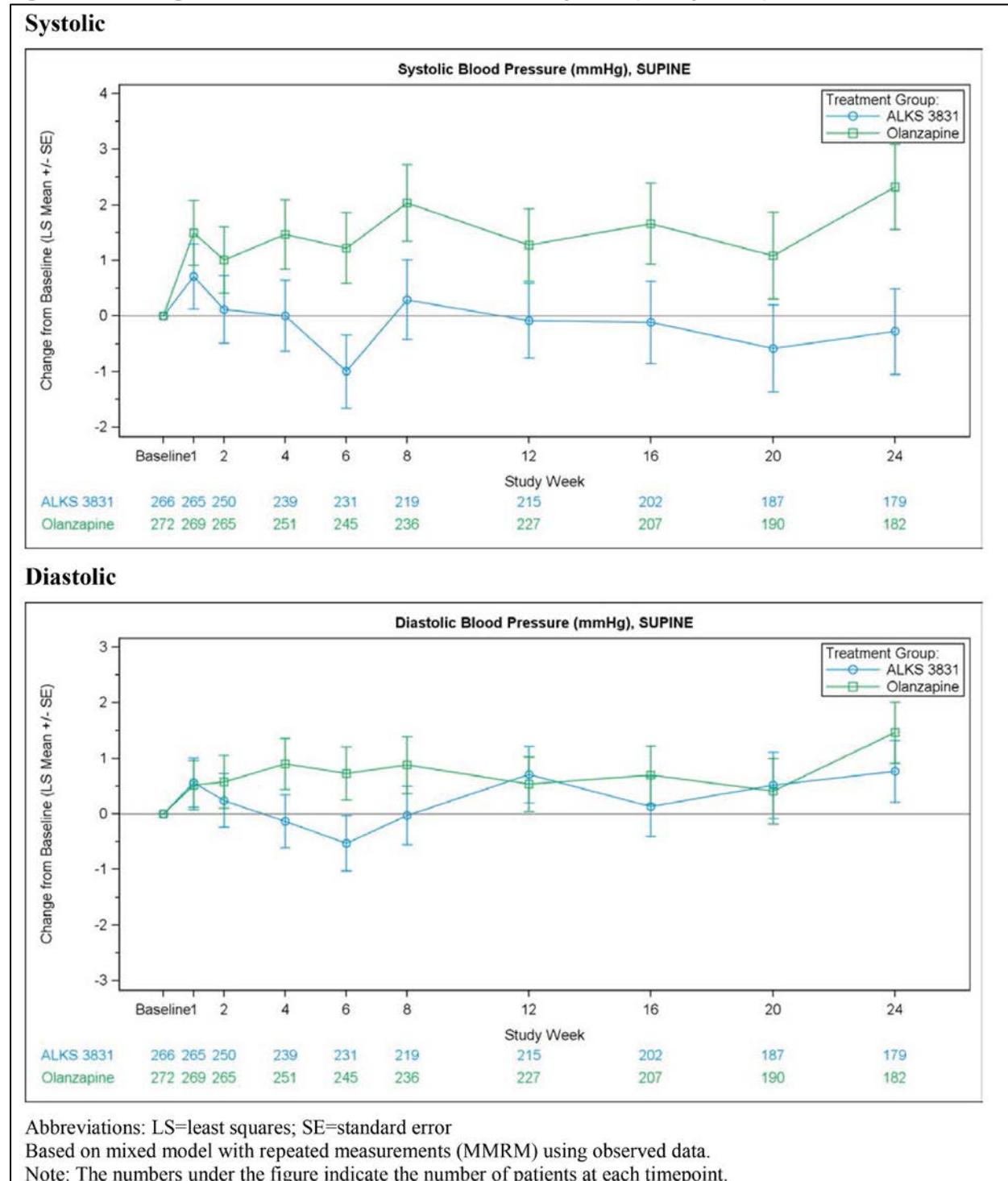
**Table 40: Blood Pressure (Study A303)**

	ALKS 3831 N=274	Olanzapine N=276
Systolic blood pressure (mmHg)		
Mean baseline (SD)	121.6 (12.88)	121.8 (11.90)
Mean change from baseline (SD)	-0.4 (10.82)	2.3 (12.57)
Diastolic blood pressure (mmHg)		
Mean baseline (SD)	77.4 (9.37)	77.3 (9.70)
Mean change from baseline (SD)	0.7 (8.32)	1.6 (9.71)

Source: A303 CSR, Table 56

The Applicant reported in a post hoc analysis that the LS mean difference (ALKS 3831 – olanzapine) in systolic and diastolic BP in mmHg at eWek 24 was -2.60 (95% CI -4.73, -0.47) and -0.70 (-2.23, 0.84), respectively. In addition, a figure of blood pressure over time suggests that the separation between groups in systolic BP is seen by Week 4 and persisted across the double-blind treatment period. No consistent differences between groups were observed in diastolic BP.

**Figure 39: Change from Baseline in Blood Pressure by Visit (Study A303)**



Source: June 3, 2020 Response to Agency Request for Information dated May 7, 2020, Figure 4

No subjects in either treatment group experienced potentially clinically significant elevation of

SBP (defined as  $\geq 180$  mmHg). There were slightly more frequent AEs of increase in blood pressure in the ALKS 3831 group (3%) compared to the olanzapine group (1%). None of these subjects discontinued the study drug.

While increases of  $\sim 2$  mmHg in systolic BP can increase risk for stroke, heart attack, and death in patients with existing high blood pressure,<sup>24</sup> the outcomes of increases of this magnitude are less certain in patients who are normotensive or not at increased cardiovascular risk. Nevertheless, preventing even small increases in BP over many years, if sustained, is likely to be favorable for cardiovascular health.

#### *Dose/Dose Response*

Not applicable: Olanzapine doses were flexibly titrated within the approved range of 10 to 20 mg; there was only one dose of samidorphan studied in this trial.

#### *Durability of Response*

Randomized controlled data beyond 24 weeks are not available. See Section 8.2.4. for longer-term OL results from the extensions of A303 and A305.<sup>25</sup>

#### *Persistence of Effect*

The effect of the drug over time after treatment is stopped or withheld is not evaluable for this trial.

#### *Efficacy Results—Exploratory Patient-reported Endpoints*

At baseline, the mean IWQOL-Lite total scores were 89.6 and 88.0 for the ALKS 3831 and olanzapine groups, respectively. According to the sponsor, these high scores indicate that weight had a low impact on the subjects' quality of life at the start of the study. At Week 24, there were no differences between treatment groups in change from baseline in the IWQOL-Lite total score and all five subscales (physical function, self-esteem, sexual life, public distress, and work).

There was no difference in change from baseline to Week 24 between groups in EQ-5D-5L index score or visual analog scale.

#### *Additional Analyses*

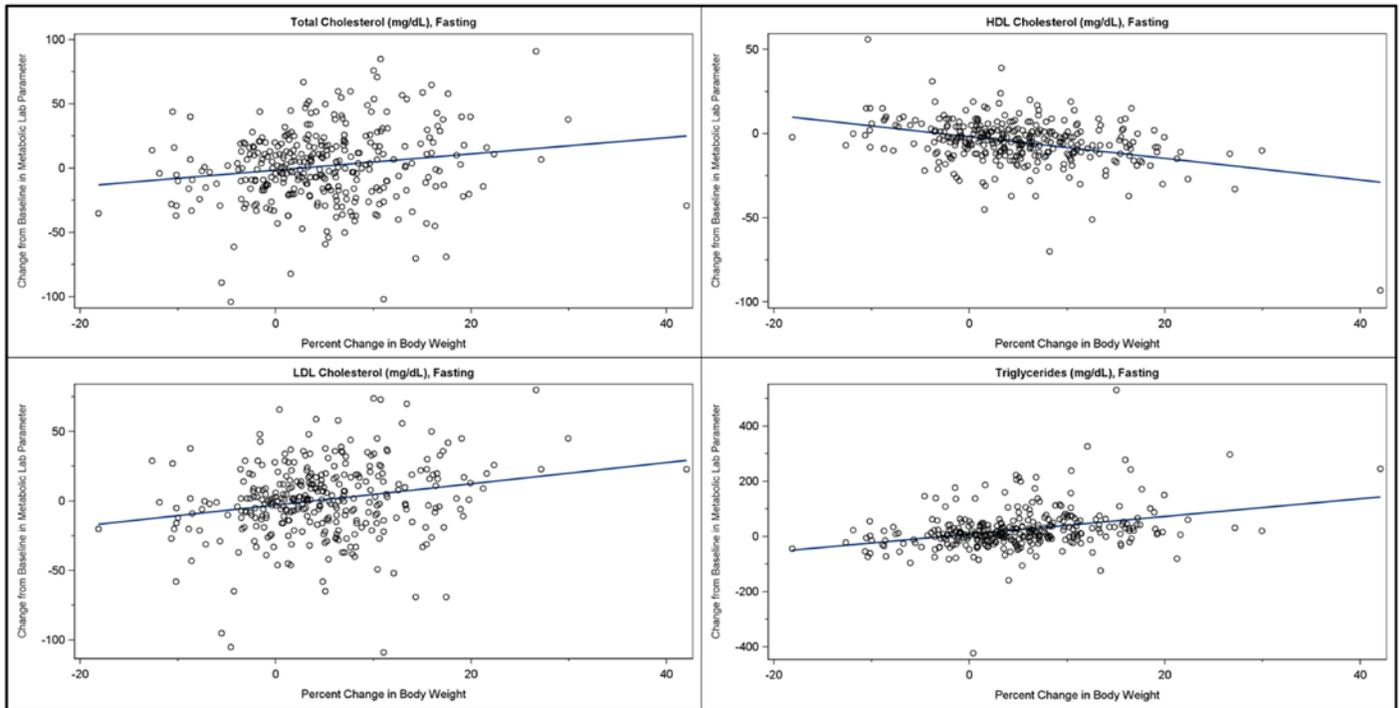
In an analysis of both treatment groups combined, increases in weight ( ) and waist circumference (not shown) corresponded to worsening of lipid parameters at Week 24.

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<sup>24</sup> FDA Draft Guidance for Industry: *Assessment of Pressor Effects of Drugs*, May 2018.

<sup>25</sup> The OL extension study for A303 is called A304, which then rolls over to a combined extension of the acute schizophrenia trial, A308. As these studies were ongoing at the time of data lock, preliminary results were provided in the integrated review of efficacy. Integrated efficacy analyses describe "durability of response" from acutely ill subjects and stable subjects separately.

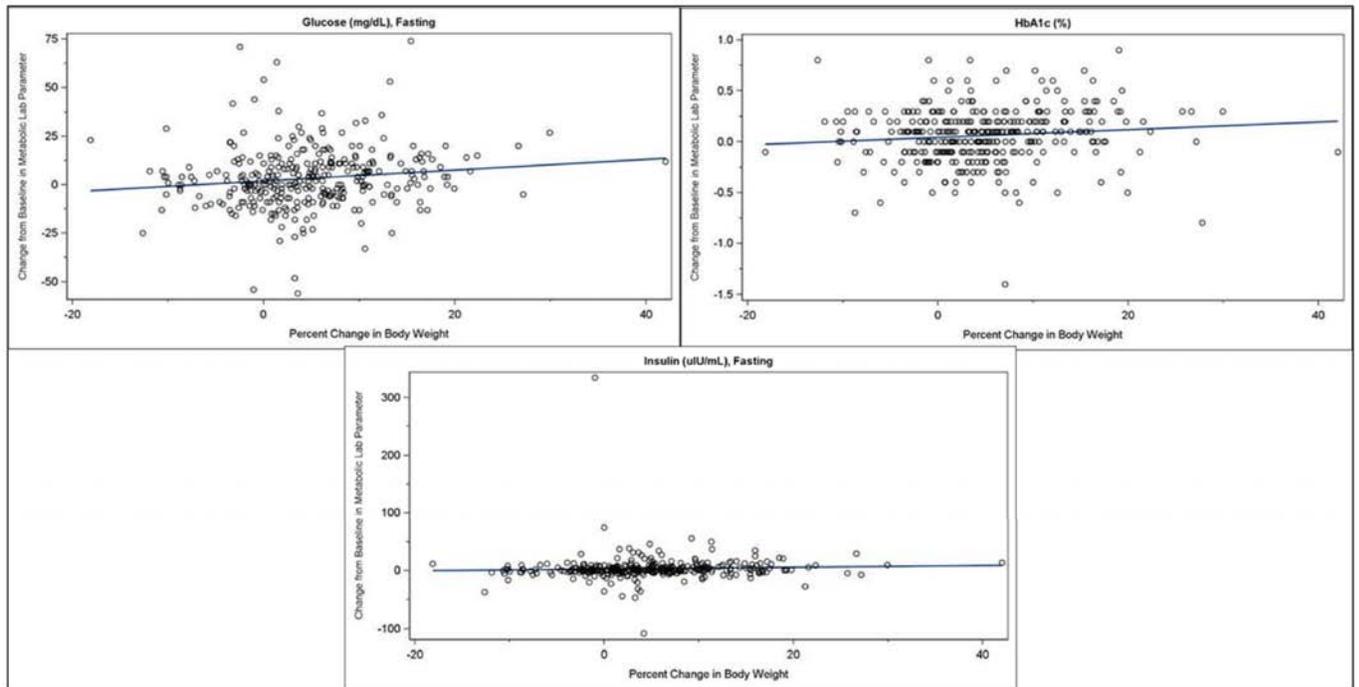
**Figure 40: Change from Baseline in Lipid Parameters vs. Percent Change from Baseline in Body Weight at Week 24 (Study A303)**



Source: A303 CSR Addendum, Figure 9

Correlations were also seen for increases in body weight and fasting glucose and HbA1c but not fasting insulin ( ). No relationship was observed for changes in waist circumference and glycemic parameters (not shown).

**Figure 41: Change from Baseline in Glycemia Parameters vs. Percent Change from Baseline in Body Weight at Week 24 (Study A303)**



Source: A303 CSR Addendum, Figure 13

The Applicant has presented these correlations to suggest that changes in body weight observed with ALKS 3831 will confer metabolic benefits in the long-term. In the reviewers' opinion, as no differences were observed in metabolic parameters between groups, and placebo-controlled data are only available for 24 weeks, the long-term clinical impact of ALKS 3831 is speculative.

### 8.2.3.2 ALK3831-302

This was a phase 2, proof-of-concept, safety, tolerability, and dose-finding, randomized, placebo-controlled, multicenter study of samidorphan in subjects with schizophrenia on olanzapine. Exploratory objectives included the assessment of weight and metabolic parameters. See Section 8.1.3 for a description of study design, and subject population disposition and characteristics.

#### Demographic and Other Baseline Characteristics

The demographics and baseline characteristics for the population of subjects who gained weight in the first week (FAS 2) were similar to the entire (FAS 1) efficacy population (see Table 23).

**Table 41: Demographic and other baseline characteristics of the FAS 2 population (Study 302)**

	Olanzapine + Placebo (N=45) n (%)	Olanzapine + Samidorphan (N=150)			Total (N=195) n (%)
		+ Samidorphan 5 mg (N=50) n (%)	+ Samidorphan 10 mg (N=53) n (%)	+ Samidorphan 20 mg (N=47) n (%)	
<b>Sex, n (%)</b>					
Male	29 (64)	35 (70)	39 (74)	36 (77)	139 (71)
Female	16 (36)	15 (30)	14 (26)	11 (23)	56 (29)
<b>Age, years</b>					
Mean (SD)	39.4 (8.5)	37.1 (8.8)	36.3 (7.6)	39.3 (8.7)	37.9 (8.4)
Median	40.0	39.0	36.0	42.0	39.0
Min, max	18, 50	18, 50	20, 49	20, 50	18, 50
<b>Race, n (%)</b>					
White	14 (31)	15 (30)	21 (40)	18 (38)	68 (35)
Black or African American	29 (64)	34 (68)	31 (59)	27 (57)	121 (62)
Asian	1 (2.2)	0	1 (2)	1 (2)	3 (2)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (2)	0	0	1 (2)	2 (1)
<b>Ethnicity, n (%)</b>					
Hispanic or Latino	1 (2)	4 (8)	3 (6)	3 (6)	11 (6)
Not Hispanic or Latino	44 (98)	46 (92)	50 (94)	44 (94)	184 (94)
<b>Region, n (%)</b>					
United States	35 (78)	44 (88)	43 (81)	41 (87)	163 (84)
Rest of the World	10 (22)	6 (12)	10 (19)	6 (13)	32 (16)
<b>Height, cm</b>					
Mean (SD)	173.3 (7.8)	173.0 (11.3)	173.7 (9.8)	173.3 (9.9)	173.4 (9.8)
Median	172.0	175.2	174.3	174.0	174.0
Min, max	155, 191	149, 201	151, 190	150, 193	149, 201
<b>Weight, kg</b>					
Mean (SD)	74.5 (13.2)	78.1 (13.3)	74.2 (12.7)	74.6 (13.1)	75.4 (13.1)
Median	77.3	77.5	73.7	72.0	75.3
Min, max	51, 95	45, 102	47, 102	49, 98	45, 102
<b>BMI, kg/m<sup>2</sup></b>					
Mean (SD)	24.7 (3.6)	26.0 (3.2)	24.5 (3.2)	24.8 (3.6)	25.0 (3.4)
Median	25.1	27.0	23.7	25.3	25.4
Min, max	18, 30	19, 30	18, 29	18, 30	18, 30
<b>BMI Group, n (%)</b>					
Underweight (<18.5)	1 (2)	0	1 (2)	1 (2)	3 (2)
Normal (18.5 to <25)	21 (47)	17 (34)	29 (55)	22 (47)	89 (46)
Overweight (25 to <30)	23 (51)	31 (62)	23 (43)	23 (49)	100 (51)
Obese (≥30)	0	2 (4)	0	1 (2)	3 (2)

Source: 302 CSR, Table 14.1.2.3.E

**Efficacy Results—Weight-Related Endpoints**

This review will focus on the randomized, controlled portion of the trial (Part A). In the FAS 1 population, the addition of samidorphan (any dose) mitigated the weight gain from baseline observed with treatment with olanzapine over the 12 weeks of the randomized trial (-1.5%, 95% CI -2.5, -0.4). This treatment difference was *not* observed in a dose-dependent manner for

the population overall. However, there is evidence of a dose response in the early weight gain (FAS 2) subpopulation ().

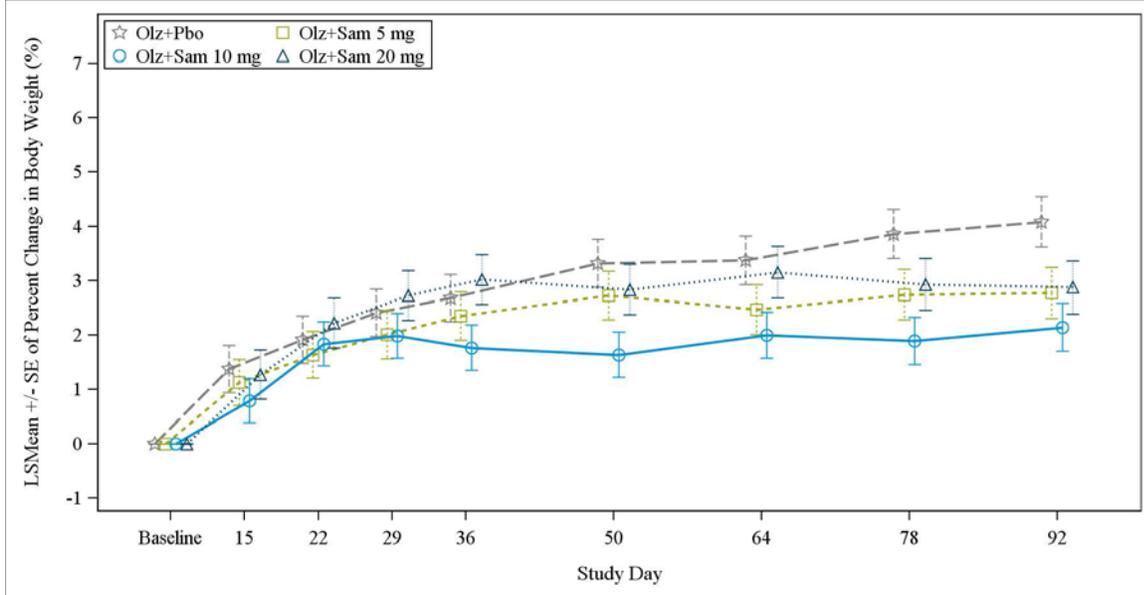
**Table 42: Percent Change in Body Weight at Day 92 (Part A; FAS 1 and FAS 2 Populations) (Study 302)**

	Olanzapine + Placebo	Olanzapine + Samidorphan			+ Any Samidorphan
		+ Samidorphan 5 mg	+ Samidorphan 10 mg	+ Samidorphan 20 mg	
FAS 1, N	74	75	83	67	225
Baseline (BL), mean (SD)	76.0 (12.4)	78.3 (13.9)	77.4 (13.6)	75.8 (12.7)	77.2 (13.4)
% change from BL at Day 92, mean (SD)	4.3 (7.1)	2.7 (5.0)	2.1 (5.7)	3.0 (6.0)	2.6 (5.6)
% change from BL at Day 92, LS mean (SD)	4.1 (0.46)	2.8 (0.48)	2.1 (0.44)	2.9 (0.48)	2.6 (0.27)
95% CI of LS mean	3.2, 5.0	1.8, 3.7	1.3, 3.0	1.9, 3.8	2.1, 3.1
OLZ+SAM – OLZ+PBO, LS mean (SE)		-1.3 (0.66)	-1.9 (0.64)	-1.2 (0.67)	-1.5 (0.54)
95% CI of LS mean difference		-2.6, 0.0	-3.2, -0.7	-2.5, 0.1	-2.5, -0.4
FAS 2, N	45	50	53	46	149
Baseline (BL), mean (SD)	75.8 (13.3)	79.6 (14.2)	75.6 (12.7)	75.5 (13.1)	76.9 (13.4)
% change from BL at Day 92, mean (SD)	5.7 (7.5)	3.8 (4.5)	1.9 (5.7)	1.7 (4.6)	2.4 (5.0)
% change from BL at Day 92, LS mean (SD)	5.3 (0.67)	3.8 (0.57)	2.2 (0.55)	1.6 (0.57)	2.6 (0.32)
95% CI of LS mean	4.2, 6.4	2.7, 4.9	1.2, 3.3	0.5, 2.7	1.9, 3.2
OLZ+SAM – OLZ+PBO, LS mean (SE)		-1.4 (0.80)	-3.0 (0.79)	-3.7 (0.81)	-2.7 (0.65)
95% CI of LS mean difference		-3.0, 0.1	-4.6, -1.5	-5.3, -2.1	-4.0, -1.4

Source: 302 CSR, Table 17

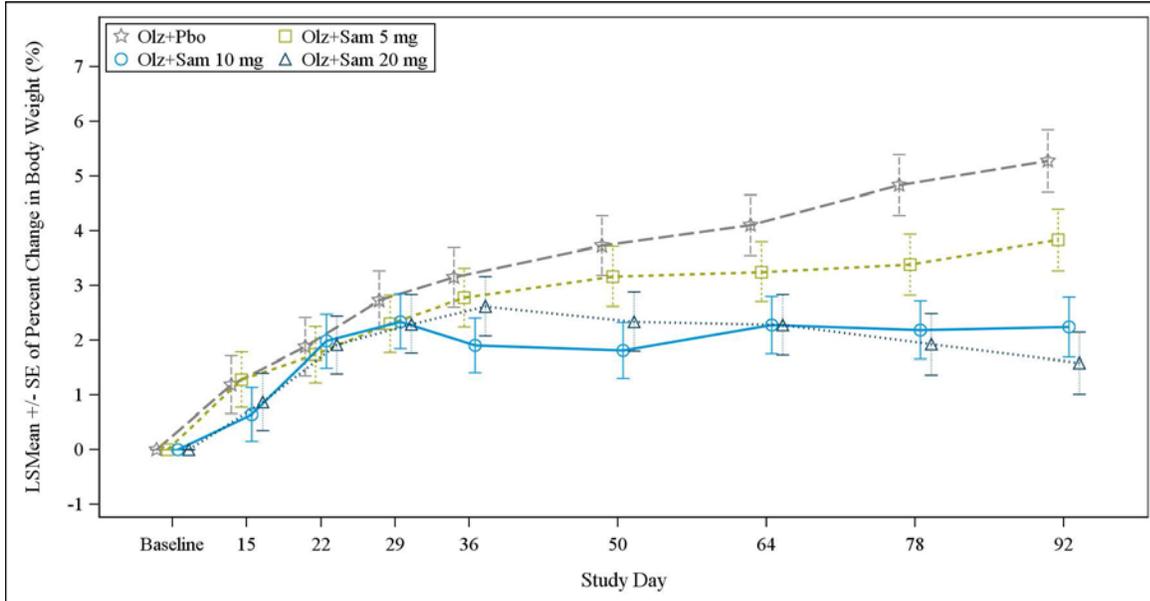
The figures below show the trajectory of weight gain for the treatment arms over the 12 week period overall (FAS 1) and in the subpopulation of subjects with early weight gain (FAS 2). The olanzapine + samidorphan arms appear to separate from olanzapine + placebo after about Day 36, particularly in the FAS 2 population.

**Figure 42: Percent Change in Body Weight by Treatment Group, Part A FAS 1 (Study 302)**



Source: 302 CSR, Figure 7

**Figure 43: Percent Change in Body Weight by Treatment Group, Part A FAS 2 (Study 302)**



Source: 302 CSR, Figure 9

In this trial, the Applicant defined significant weight gain for the purposes of categorical analyses as those of body weight change of  $\geq 5\%$ ,  $\geq 7\%$  or  $\geq 10\%$  from baseline. Note that these analyses are conducted on completers and do not impute values for subjects with missing data at the Day 92 timepoint. The proportion of completers with  $\geq 10\%$  weight gain was numerically

smaller for the comparisons of OLZ+SAM overall vs. OLZ+PBO (confidence intervals and p-values not shown).

**Table 43: Categorical Weight Gain Assessment at Day 92 (Proportion of Subjects Meeting Criteria) (Study 302)**

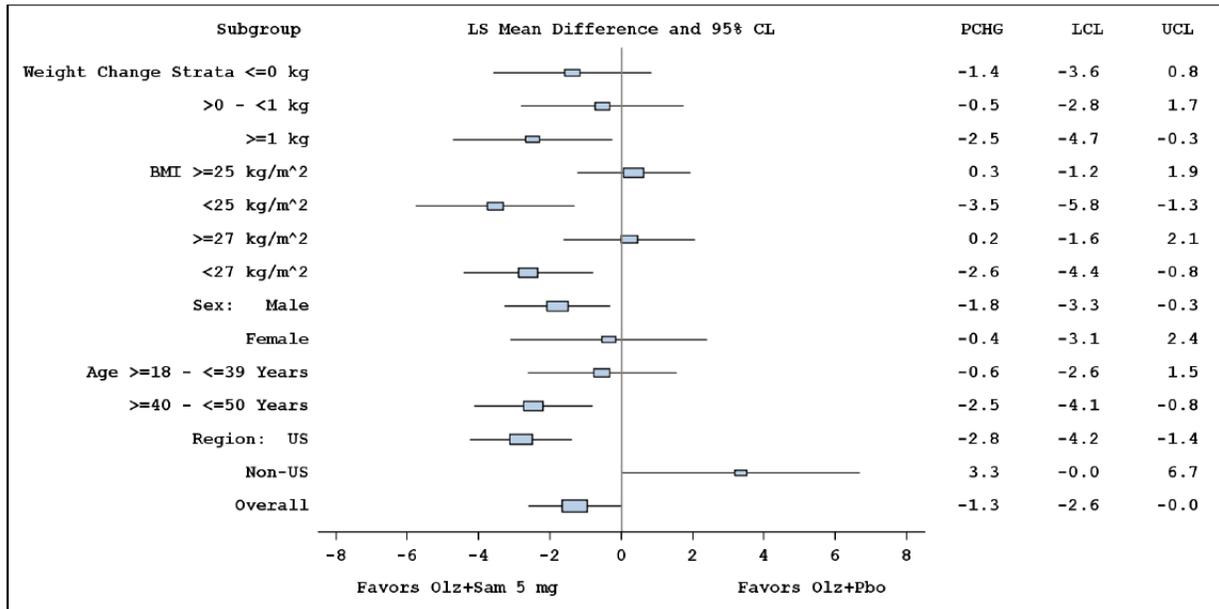
	Olanzapine + Placebo	Olanzapine + Samidorphan			+ Any Samidorphan
		+ Samidorphan 5 mg	+ Samidorphan 10 mg	+ Samidorphan 20 mg	
FAS 1, N completers	56	52	59	54	165
≥ 5% weight gain n (%)	20 (36)	18 (35)	16 (27)	16 (30)	50 (30)
≥ 7% weight gain n (%)	14 (25)	8 (15)	9 (15)	12 (22)	29 (18)
≥ 10% weight gain n (%)	10 (18)	3 (6)	4 (7)	5 (9)	12 (7)
FAS 2, N completers	35	35	36	35	106
≥ 5% weight gain n (%)	14 (40)	13 (37)	8 (22)	8 (23)	29 (27)
≥ 7% weight gain n (%)	11 (31)	7 (20)	4 (11)	7 (20)	18 (17)
≥ 10% weight gain n (%)	8 (23)	3 (9)	3 (8)	1 (3)	7 (7)

Source: 302 CSR, Table 19

### Subgroups

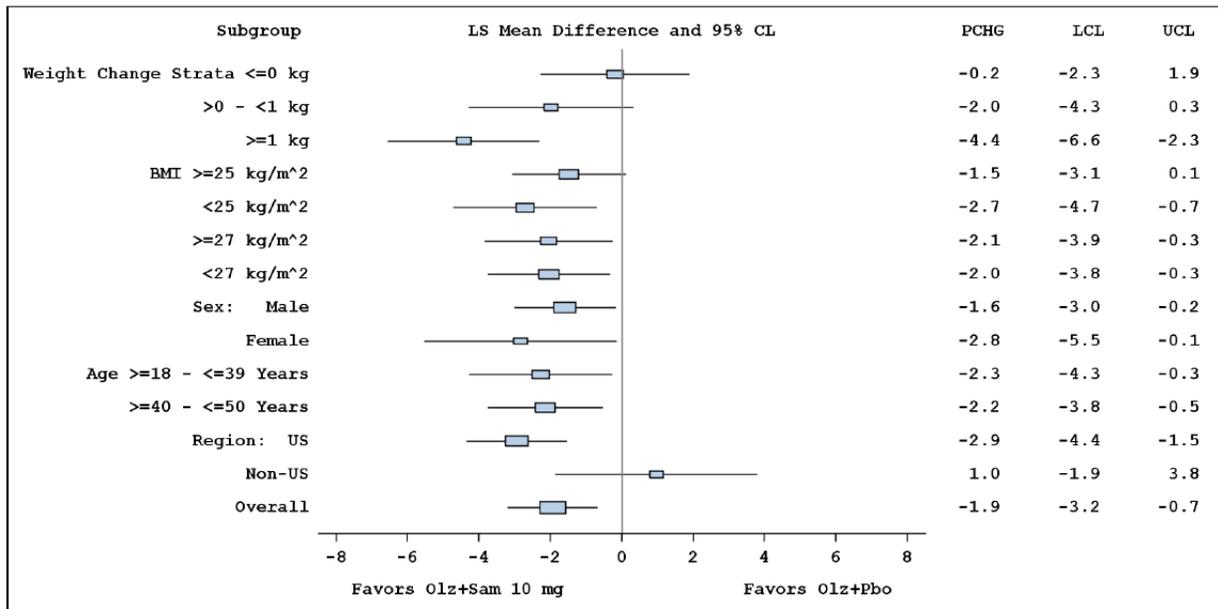
The following figures present the subgroup analyses for the percent change in body weight at Day 92 for each of the olanzapine + samidorphan doses vs. olanzapine + placebo and for the combined olanzapine + samidorphan group vs. olanzapine + placebo. Of particular interest are the lead-in weight gain strata and the baseline BMI subgroups. A trend for increased treatment effect with olanzapine + samidorphan (10 mg, 20 mg, and overall) was observed in two subgroups of interest: 1) the subgroup of subjects with weight gain of at least 1 kg in the olanzapine lead-in week, and 2) the subgroup of subjects with baseline BMI less than 25 kg/m<sup>2</sup>. This is consistent with the observed weight gain with olanzapine (most weight gain observed early and in patients with lowest BMIs) and could potentially identify a patient population more likely to achieve benefit with the addition of samidorphan in future trials.

**Figure 44: Forest Plot of Percent Change in Body Weight (%) at Day 92, OLZ + SAM 5 mg vs. OLZ + PBO (Study 302)**



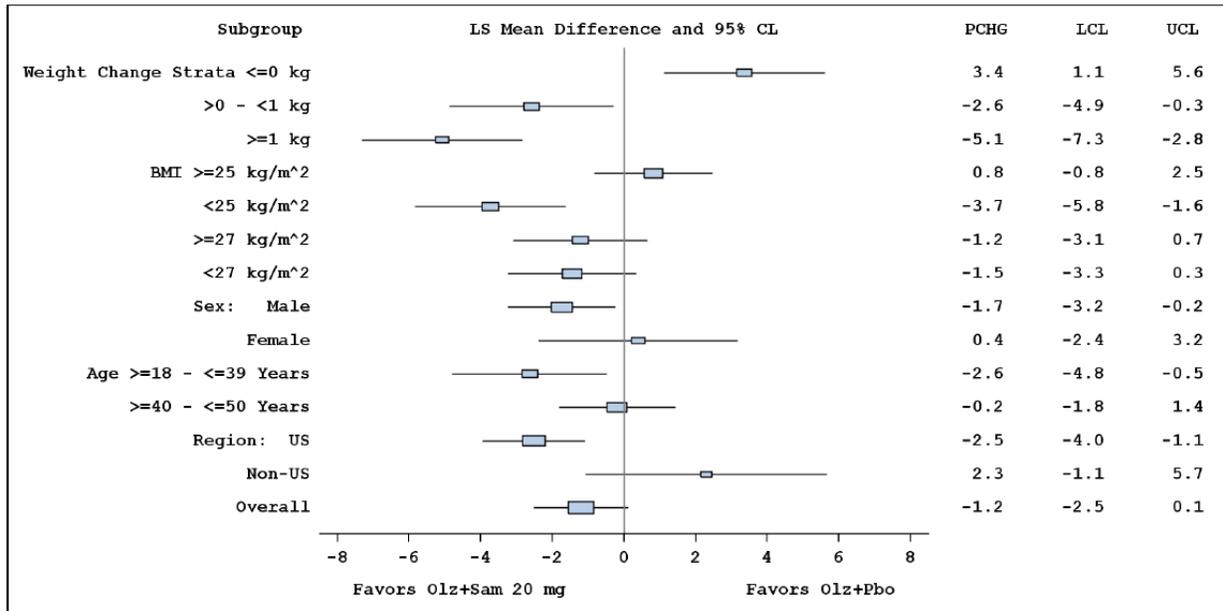
Source: 302 CSR, Figure 14.2.3.1.1A.E

**Figure 45: Forest Plot of Percent Change in Body Weight (%) at Day 92, OLZ + SAM 10 mg vs. OLZ + PBO (Study 302)**



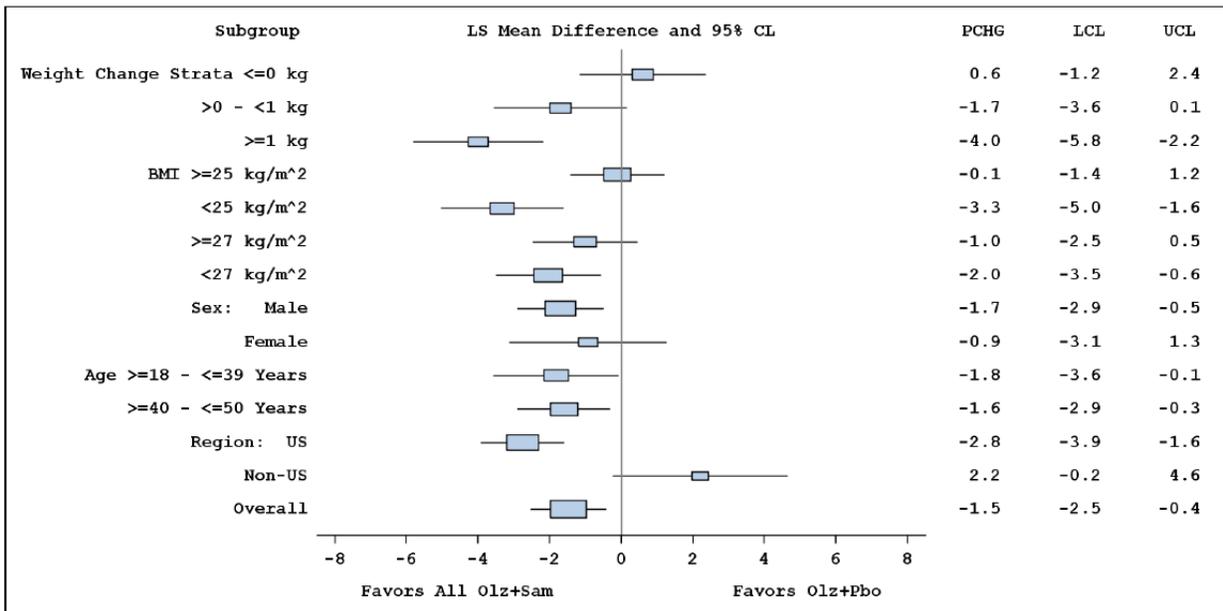
Source: 302 CSR, Figure 14.2.3.1.1A.E

**Figure 46: Forest Plot of Percent Change in Body Weight (%) at Day 92, OLZ + SAM 20 mg vs. OLZ + PBO (Study 302)**



Source: 302 CSR, Figure 14.2.3.1.1A.E

**Figure 47: Forest Plot of Percent Change in Body Weight (%) at Day 92, All OLZ + SAM vs. OLZ + PBO (Study 302)**



Source: 302 CSR, Figure 14.2.3.1.1A.E

Efficacy Results—Other Relevant Endpoints

No differences between groups were observed in waist circumference in Part A. For the FAS 1 analysis, the LS mean difference for the pooled ALKS 3831 group versus the olanzapine only group was -0.1 (95% CI: -1.1, 0.8), and for the FAS 2 analysis, the LS mean difference for the pooled ALKS 3831 group versus the olanzapine only group was 0.1 (95% CI: -1.2, 1.3); there was no observed difference among treatment arms ().

**Table 44: Change in Waist Circumference at Day 92, Part A (Study 302)**

	Statistics	Olz+Pbo	Olz+Sam 5 mg	Olz+Sam 10 mg	Olz+Sam 20 mg	All Olz+Sam
<b>FAS 1 Population</b>	N	74	75	83	68	226
	Baseline, mean (SD)	90.8 (9.76)	91.9 (10.98)	90.1 (10.77)	90.0 (11.35)	90.7 (11.00)
	Change from baseline at Day 92, mean (SD)	1.9 (4.83)	0.9 (4.08)	1.4 (4.80)	2.4 (4.83)	1.6 (4.61)
	LS mean (SE)	1.7 (0.43)	0.9 (0.44)	1.3 (0.41)	2.4 (0.44)	1.5 (0.25)
	LS mean difference (SE) vs. Olz+Pbo		-0.7 (0.62)	-0.4 (0.60)	0.7 (0.61)	-0.1 (0.50)
	95% CI of LS Mean Difference		(-2.0, 0.5)	(-1.5, 0.8)	(-0.5, 1.9)	(-1.1, 0.8)
<b>FAS 2 Population</b>	N	45	50	53	47	150
	Baseline, mean (SD)	90.0 (9.67)	93.0 (10.98)	88.5 (10.65)	89.6 (11.59)	90.3 (11.15)
	Change from baseline at Day 92, mean (SD)	2.2 (5.21)	1.7 (4.46)	1.8 (5.19)	2.1 (4.23)	1.8 (4.60)
	LS Mean (SE)	1.8 (0.55)	1.8 (0.55)	1.8 (0.54)	2.1 (0.55)	1.9 (0.32)
	LS Mean Difference (SE) vs. Olz+Pbo		-0.0 (0.78)	0.0 (0.77)	0.2 (0.78)	0.1 (0.64)
	95% CI of LS Mean Difference		(-1.6, 1.5)	(-1.5, 1.5)	(-1.3, 1.8)	(-1.2, 1.3)

Abbreviations: LS=least square; Olz=olanzapine; Pbo=placebo; Sam=samidorphan; SD=standard deviation; SE=standard error

Note: The MMRM model uses the change from baseline in waist circumference at each post-baseline visit as the dependent variable, and includes lead-in weight gain strata, treatment group, visit, and treatment group-by-visit interaction as factors and baseline waist circumference as a covariate.

Note: Baseline is defined as the last non-missing value on or before the date of the first dose of samidorphan/placebo.

Source: Study 302 CSR, Table 21

*Dose/Dose Response*

As the above analyses demonstrate in the FAS 1 population, a dose response in weight for samidorphan when added to olanzapine was *not* observed (numerically, samidorphan 20 mg had the least effect, and samidorphan 10 mg had the greatest). This could be due to insufficient power to demonstrate small differences between groups, a ceiling effect with the 20 mg dose, chance, or a true benefit of the 10 mg dose over the other doses. Since only the 10 mg dose was studied in the pivotal phase 3 weight gain trial A303 (discussed above), this pattern could not be confirmed.

Of interest, in the FAS 2 population, a group of subjects who gained weight early on olanzapine, an apparent dose-response with samidorphan was observed (see , above). This could suggest a possible patient population who would be more likely to benefit from the addition of samidorphan, or this pattern could have been due to chance. As subjects who gained early weight on olanzapine alone were not randomized into Study A303, this pattern could not be confirmed.

*Durability of Response*

Prolonged drug effect (past 12 weeks/92 days) was described in the open-label portion of the study (Part B), in which olanzapine + placebo was switched to olanzapine + samidorphan 20 mg, and the other arms remained on the same treatment. In general, mean weight was essentially unchanged during the period from Day 92 to Day 176 (mean ± 0.2 kg), with the exception of the samidorphan 10 mg arm, which gained only slightly more, with a mean of +0.9 kg (1.2%) during this period. Note that this analysis and its interpretation is limited by the all-active treatment nature of the study period (i.e., no olanzapine-only arm), as well as the fact that only a subset of subjects entered Part B. Additional discussion of the limitations of the longer-term data can be found in Section 8.2.4.

**Table 45: Absolute and Percent Change in Body Weight from Part B Baseline to Day 176, FAS 1 and FAS 2 Populations Who Entered Part B (Study 302)**

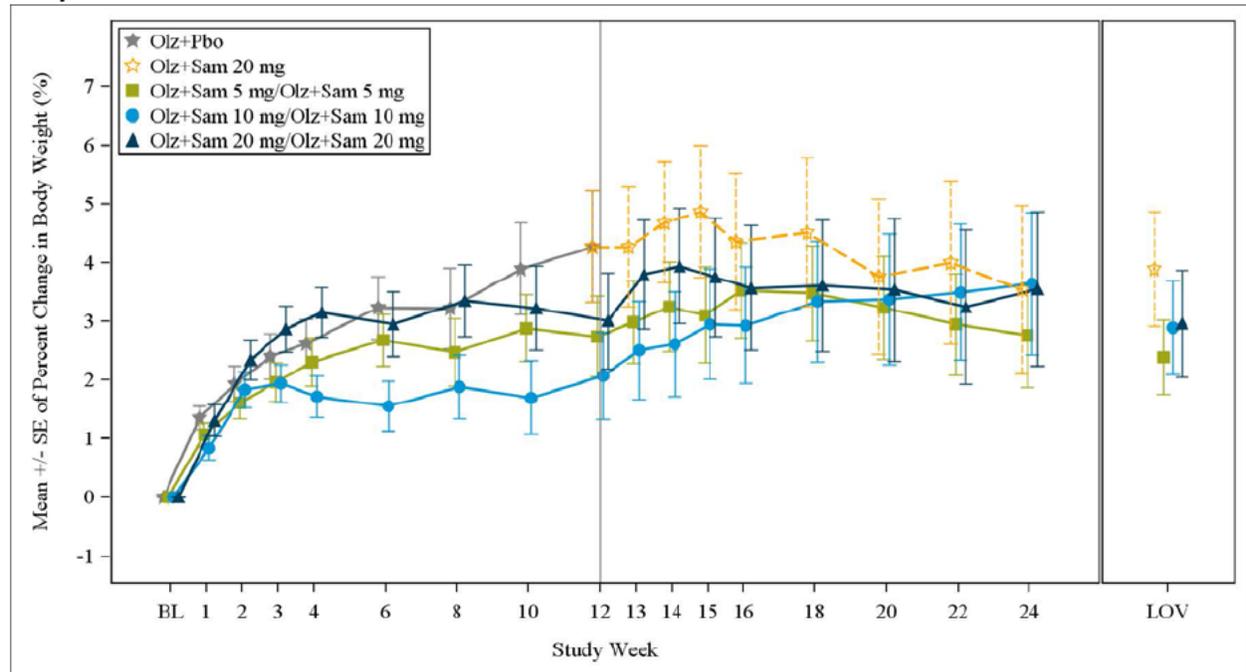
Part A Treatment	Olanzapine + Placebo	Olanzapine + Samidorphan 5 mg	Olanzapine + Samidorphan 10 mg	Olanzapine + Samidorphan 20 mg	Olanzapine + Any Samidorphan
Part B Treatment	Olanzapine + Samidorphan 20 mg	Olanzapine + Samidorphan 5 mg	Olanzapine + Samidorphan 10 mg	Olanzapine + Samidorphan 20 mg	Olanzapine + Any Samidorphan in Part A
FAS 1, N	54	52	57	54	163
Part B baseline, mean (SD)	78.8 (13.3)	79.4 (14.7)	78.6 (14.4)	77.9 (14.0)	78.6 (14.3)
Abs. change mean (SD)	0.1 (2.9)	-0.2 (2.9)	0.9 (3.8)	0.2 (2.9)	0.4 (3.3)
Pct. change mean (SD)	0.1 (3.6)	-0.1 (3.6)	1.2 (4.7)	0.2 (3.6)	0.5 (4.1)
FAS 2, N	33	35	34	35	104
Part B baseline, mean (SD)	80.0 (14.0)	81.0 (15.0)	76.0 (12.6)	76.9 (14.2)	78.0 (14.0)
Abs. change mean (SD)	0.2 (3.3)	-0.5 (2.6)	0.9 (3.6)	0.1 (2.8)	0.1 (3.0)
Pct. change mean (SD)	0.2 (4.0)	-0.5 (3.0)	1.2 (4.3)	-0.0 (3.6)	0.2 (3.7)

Source: Study 302 CSR, Table 27

The following figures illustrate weight change over time among the treatment arms in Parts A

and B. It is noted that the mean weight in the olanzapine + samidorphan 10 mg group increases over the Part B period to achieve a similar mean weight at Week 24 as the other olanzapine + samidorphan groups. Note also that interpretation of these data is limited by subject attrition over time; see the numbers of subjects with available body weight by visit in .

**Figure 48: Summary of Percent Change in Body Weight by Visit, Parts A and B, FAS 1 (Study 302)**



BL=Baseline, LOV=Last observed value

Source: 302 CSR, Figure 14.2.2.1.C

**Table 46: Number of Subjects with Body Weight Assessment by Visit (Study 302)**

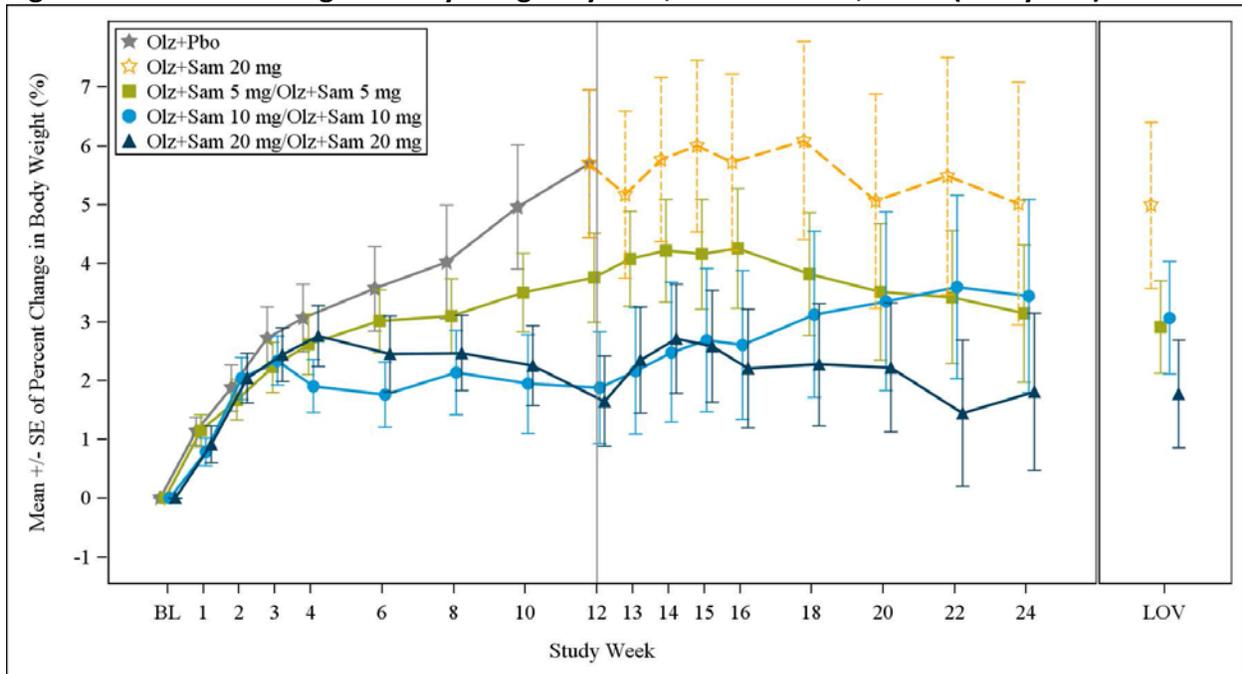
Treatment Part A (Olanzapine +)	Treatment Part B (Olanzapine +)	BL	Week 6	Week 12	Week 18	Week 24	LOV
Placebo	Samidorphan 20 mg	74	63	56	47	45	54
Samidorphan 5 mg	Samidorphan 5 mg	75	60	52	48	46	52
Samidorphan 10 mg	Samidorphan 10 mg	83	72	59	52	52	57
Samidorphan 20 mg	Samidorphan 20 mg	67	60	54	47	45	54

BL=Baseline, LOV=Last observed value

Source: Response to Agency Request for Information dated 07 May 2020 – Part 1, Table 2

(FAS 2, Parts A and B) suggests that in the early weight gain subgroup, the addition of samidorphan to olanzapine in Part B may mitigate additional weight gain; however, without a randomized olanzapine-only arm, long-term weight changes are speculative.

**Figure 49: Percent Change in Body Weight by Visit, Parts A and B, FAS 2 (Study 302)**



Source: 302 CSR, Figure 14.2.2.2.C

#### *Persistence of Effect*

No analyses were conducted to assess the effect on weight after samidorphan was discontinued or withheld.

#### *Efficacy Results—Secondary/Exploratory COA (PRO) Endpoints*

The Impact of Weight on Quality-of-Life (IWQOL)-Lite scale was administered at Baseline and Day 92 to assess a subject's perception of how their weight affects their daily quality-of-life in five domains (physical function, self-esteem, sexual life, public distress, and work). Items were rated on a 5-point response scale ranging from "always true" (5 points) to "never true" (1 point). The raw scores were transformed for analysis with scores ranging from 0 to 100, with lower scores indicating more impaired quality-of-life. At baseline, IWQOL-Lite total scores were high (>90) for all arms. Although numerically, the samidorphan groups appeared to have a small attenuation in IWQOL decrease, only descriptive statistics were provided. As the FAS 2 population results were similar to FAS 1, only FAS 1 is presented here.

**Table 47: IWQoL-Lite Total Score and Subscale Changes (Study 302)**

	Olanzapine + Placebo N=74	Olanzapine + Samidorphan			+ Any Samidorphan N=226
		+ Samidorphan 5 mg N=75	+ Samidorphan 10 mg N=83	+ Samidorphan 20 mg N=68	
<b>Total Score</b>					
Baseline, mean (SD)	91.3 (15.3)	94.8 (9.9)	93.0 (10.8)	93.0 (12.9)	93.6 (11.2)
Change from BL to Day 92, mean (SD)	-4.2 (12.8)	-0.9 (8.3)	-0.8 (9.1)	0.9 (7.6)	-0.2 (8.4)
<b>Physical Function</b>					
Baseline, mean (SD)	90.4 (15.3)	93.5 (10.8)	92.8 (11.3)	91.8 (13.0)	92.8 (11.7)
Change from BL to Day 92, mean (SD)	-5.8 (16.0)	-1.4 (11.4)	-1.2 (10.6)	0.9 (10.9)	-0.6 (10.9)
<b>Self-Esteem</b>					
Baseline, mean (SD)	89.5 (18.8)	93.9 (15.3)	90.4 (16.7)	92.0 (18.4)	92.0 (16.8)
Change from BL to Day 92, mean (SD)	-4.5 (15.4)	-1.2 (12.3)	-1.1 (13.3)	0.4 (11.3)	-0.6 (12.3)
<b>Sexual Life</b>					
Baseline, mean (SD)	92.2 (19.0)	95.3 (11.9)	93.0 (17.6)	92.5 (18.0)	93.6 (16.0)
Change from BL to Day 92, mean (SD)	-4.8 (22.6)	0.8 (7.4)	-0.8 (19.1)	1.8 (14.6)	0.6 (14.7)
<b>Public Distress</b>					
Baseline, mean (SD)	93.4 (16.2)	97.0 (9.4)	96.0 (10.2)	96.0 (12.3)	96.3 (10.6)
Change from BL to Day 92, mean (SD)	-0.5 (12.4)	0.0 (5.4)	0.2 (11.6)	0.9 (5.2)	0.4 (8.1)
<b>Work</b>					
Baseline, mean (SD)	93.2 (18.5)	96.2 (11.2)	94.7 (11.8)	95.0 (13.5)	95.3 (12.1)
Change from BL to Day 92, mean (SD)	-3.0 (18.5)	-0.7 (9.7)	-0.6 (13.0)	1.1 (8.6)	-0.1 (10.6)

Source: 302 CSR, Table 22

A questionnaire designed to assess subject-specific craving of 28 food items (Food Craving Inventory, FCI) was administered at baseline, Day 15, and Day 92. Craving for the specified food items was rated on a 5-point scale ranging from “never” (1 point) to “always” (5 points). The total score and the subscores (including high fat, sweets, carbohydrate/starch, and fast food fats) are the average response of corresponding items and was calculated for each treatment group with a possible score range of 1 to 5. Only descriptive statistics were provided, and all changes among groups at both timepoints were small. At Day 15, mean change from baseline in the olanzapine + placebo group was -0.07 and in the olanzapine + samidorphan 10 group +0.08; at Day 92, mean change from baseline in the olanzapine + placebo group was -0.02 and in the olanzapine + samidorphan 10 group +0.09.

*Additional Analyses Conducted on the Individual Trial*

Metabolic and blood pressure parameters were considered safety endpoints in this trial and are reported here descriptively.

Lipid and glycemic laboratory values were normal at baseline and changed small amounts over the 12-week randomized period, generally not in a dose-related fashion. Potentially adverse findings were seen with increases in fasting glucose (16% of patients on olanzapine vs. approximately 32% of patients on OLZ/SAM 10 and OLZ/SAM 20 reported increases in fasting glucose of at least 10 mg/dL at any post-baseline visit).

**Table 48: Changes in Metabolic Parameters, Part A, Safety Population (Study 302)**

	Olanzapine + Placebo N=74	Olanzapine + Samidorphan			+ Any Samidorphan N=234
		+ Samidorphan 5 mg N=80	+ Samidorphan 10 mg N=86	+ Samidorphan 20 mg N=68	
Total cholesterol, fasting, mg/dL					
Baseline, mean (SD)	174.6 (30.1)	176.4 (34.7)	175.1 (29.5)	170.0 (31.7)	174.1 (32.0)
Change from BL to last post-BL, mean (SD)	8.5 (27.4)	5.1 (27.2)	3.5 (29.5)	4.6 (24.8)	4.4 (27.3)
Normal (<200) to High (≥240), n/n relevant population (%)	3/37 (8)	1/37 (3)	3/43 (7)	2/44 (5)	6/124 (5)
Increase ≥ 40 mg/dL, n/n relevant population (%)	8/50 (16)	4/48 (8)	5/54 (9)	5/54 (9)	14/156 (9)
LDL-C, fasting, mg/dL					
Baseline, mean (SD)	103.1 (24.7)	106.5 (33.0)	105.3 (31.1)	99.0 (26.2)	103.9 (30.5)
Change from BL to last post-BL, mean (SD)	11.5 (21.9)	5.8 (23.1)	6.5 (20.0)	10.3 (20.9)	7.4 (21.3)
Normal (<100) to High (≥160), n/n relevant population	0/21	0/20	0/27	0/24	0/71
Increase ≥ 30 mg/dL, n/n relevant population (%)	14/50 (28)	9/48 (19)	7/54 (13)	9/54 (17)	25/156 (16)
HDL-C, fasting, mg/dL					
Baseline, mean (SD)	53.5 (14.7)	52.2 (16.2)	52.6 (17.7)	50.1 (14.9)	51.7 (16.4)
Change from BL to last post-BL, mean (SD)	-3.2 (9.4)	-2.0 (9.1)	-1.6 (12.9)	-2.9 (7.3)	-2.1 (10.3)
Normal (≥40) to Low (<40), n/n relevant population (%)	3/41 (7)	7/40 (18)	8/41 (20)	4/37 (11)	19/118 (16)
Decrease ≥ 20 mg/dL, n/n relevant population (%)	5/50 (10)	0/48	3/54 (6)	1/54 (2)	4/156 (3)
Triglycerides, fasting, mg/dL					
Baseline, mean (SD)	119.4 (72.7)	114.9 (68.8)	120.3 (90.3)	123.4 (90.4)	119.4 (83.3)
Change from BL to last post-BL, mean (SD)	6.5 (75.6)	20.4 (60.5)	-6.2 (95.5)	-0.7 (78.3)	4.0 (80.9)
Normal (<150) to High (≥200), n/n relevant population (%)	1/38 (3)	3/36 (8)	3/43 (7)	5/41 (12)	11/120 (9)
Increase ≥ 50 mg/dL, n/n relevant population (%)	8/50 (16)	11/48 (23)	9/54 (17)	8/54 (15)	28/156 (18)

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	Olanzapine + Placebo N=74	Olanzapine + Samidorphan			+ Any Samidorphan N=234
		+ Samidorphan 5 mg N=80	+ Samidorphan 10 mg N=86	+ Samidorphan 20 mg N=68	
Glucose, fasting, mg/dL					
Baseline, mean (SD)	92.6 (13.32)	89.9 (12.46)	92.2 (15.97)	90.9 (10.71)	91.0 (13.40)
Change from BL to last post-BL, mean (SD)	4.1 (20.21)	3.8 (21.04)	7.0 (34.05)	5.2 (17.44)	5.4 (25.77)
Normal (<100) to High (≥126), n/n relevant population (%)	2/37 (5)	1/39 (3)	3/44 (7)	2/46 (4)	6/129 (5)
Increase ≥ 10 mg/dL, n/n relevant population (%)	8/49 (16)	8/47 (17)	18/57 (32)	18/55 (33)	44/159 (28)
Insulin, µU/mL					
Baseline, mean (SD)	17.1 (24.2)	16.6 (27.6)	16.8 (18.4)	16.4 (41.8)	16.6 (29.8)
Change from BL to last post-BL (SD)	10.8 (52.1)	10.6 (48.8)	0.08 (23.9)	4.7 (47.1)	5.0 (40.8)
Ratio of fasting glucose to fasting insulin, x10 <sup>6</sup>					
Baseline, mean (SD)	0.10 (0.0720)	0.09 (0.0633)	0.11 (0.1139)	0.12 (0.0745)	0.11 (0.0882)
Change from BL to last post-BL Mean, (SD)	-0.004 (0.068)	-0.012 (0.079)	-0.015 (0.093)	-0.024 (0.079)	-0.017 (0.084)
C-reactive protein, mg/dL					
Baseline, mean (SD)	0.52 (0.780)	0.57 (1.16)	0.43 (0.547)	0.47 (0.713)	0.49 (0.852)
Change from BL to last post-BL, mean, (SD)	0.02 (0.694)	-0.10 (1.23)	0.22 (1.45)	-0.16 (0.762)	-0.007 (1.21)
HbA1c, fasting, %					
Baseline, mean (SD)	5.45 (0.369)	5.39 (0.365)	5.40 (0.428)	5.46 (0.448)	5.41 (0.413)
Change from BL to last post-BL, mean (SD)	-0.05 (0.276)	-0.01 (0.227)	0.06 (0.579)	-0.04 (0.276)	0 (0.404)
Shift from <6.1% to:					
≥6.1%, n/n relevant population (%)	1/47 (2)	1/46 (2)	4/56 (7)	1/52 (2)	6/154 (4)
≥8%, n/n relevant population (%)	0/47	0/46	1/56 (2)	0/52	1/154 (1)

Source: 302 CSR, Tables 50 and 53

As this analysis was conducted on the safety population, there was no analysis conducted for FAS 1 and FAS 2. An exploratory subgroup analysis suggests a trend in favor of ALKS 3831 over olanzapine in changes in fasting triglyceride, glucose, and insulin values for the olanzapine 1-week run-in with weight gain ≥1 kg subgroup (data not shown).

Mean supine systolic and diastolic blood pressure values were normal at baseline and changed small amounts over the 12-week randomized period.

**Table 49: Change from Baseline to Last Post-Baseline Assessment for Supine Blood Pressure, Part A, Safety Population (Study 302)**

	Olanzapine + Placebo N=74	Olanzapine + Samidorphan			+ Any Samidorphan N=234
		+ Samidorphan 5 mg N=80	+ Samidorphan 10 mg N=86	+ Samidorphan 20 mg N=68	
<b>Systolic blood pressure, mmHg</b>					
Baseline, mean (SD)	120.7 (10.5)	121.4 (11.3)	121.4 (11.1)	119.4 (11.2)	120.8 (11.2)
Change from BL to last post-BL, mean (SD)	0.8 (11.8)	-0.2 (11.5)	0.5 (9.7)	1.1 (10.3)	0.4 (10.5)
<b>Diastolic blood pressure, mmHg</b>					
Baseline, mean (SD)	75.9 (8.2)	77.3 (8.5)	76.0 (8.9)	75.9 (7.6)	76.4 (8.4)
Change from BL to last post-BL, mean (SD)	0.9 (8.5)	-0.4 (9.7)	0.4 (7.9)	0.3 (7.8)	0.1 (8.5)

Source: Study 302 CSR, Table 73

No subjects were observed to have potentially clinically significant values of high systolic BP (defined as  $\geq 180$  mmHg and increase  $\geq 20$  mmHg) or diastolic BP (defined as  $\geq 105$  mmHg and increase  $\geq 15$  mmHg).

#### 8.2.4 ALK3831-A304 and ALK3831-A306

ALK3831-A304 and ALK3831-A306 were the OL extension studies of Studies A303 and A305, respectively. Enrolled subjects were assessed over 52 weeks to evaluate ALKS 3831's long-term safety and tolerability. There was no comparator arm in either long-term study.

The effect of switching from olanzapine to ALKS 3831 on weight 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 50). 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 in the double-blind period were only included if they were exposed to ALKS 3831 during the OL study—subjects taking ALKS 3831 during studies A303 or A305 were included in the switch analysis if they had post-baseline 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. Furthermore, because there is no group randomized to continue on olanzapine alone past 24 weeks, the impact of the addition of samidorphan in these subjects is speculative

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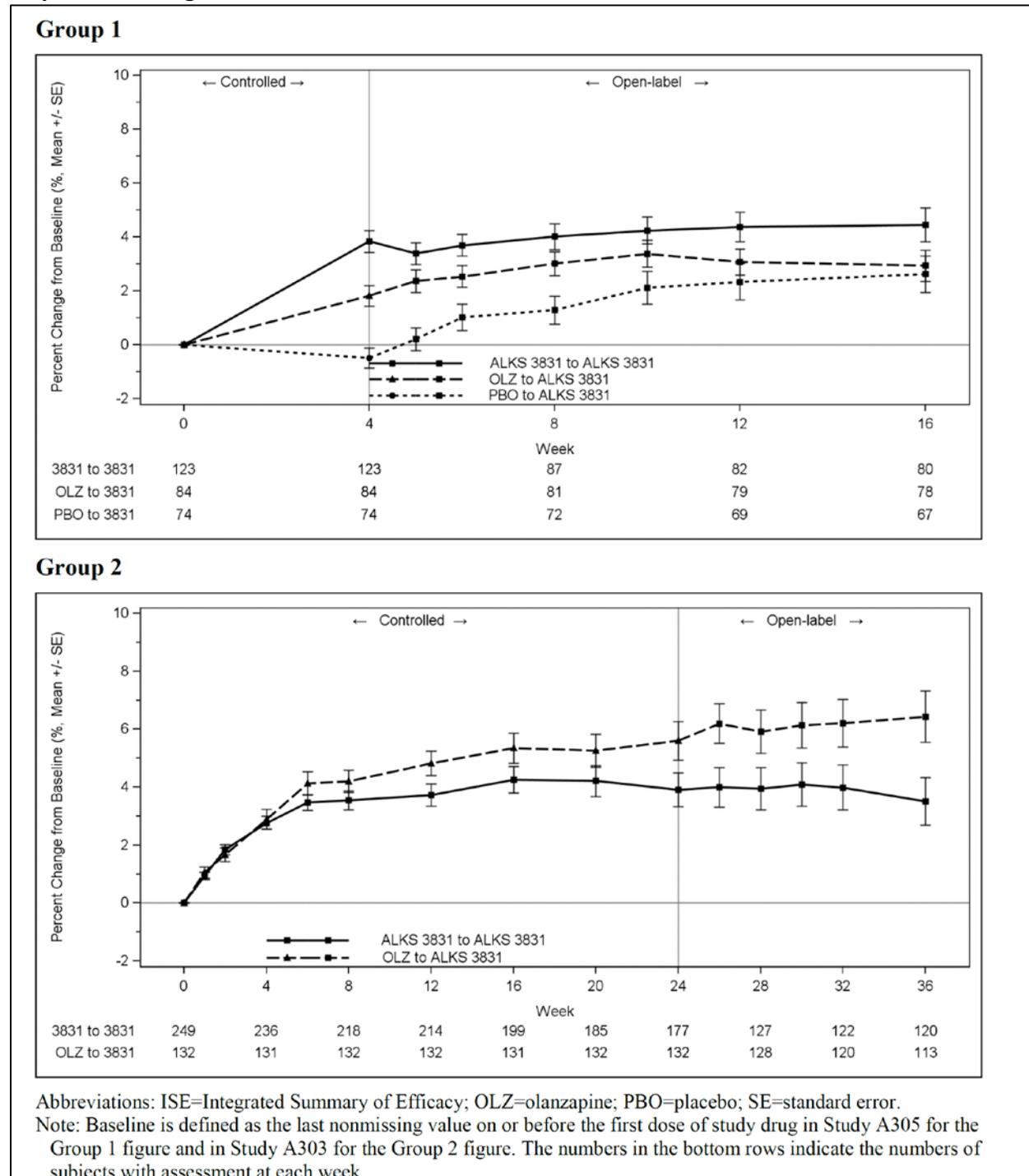
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In Group 1 (Study A306; acutely ill), the weight trajectories of subjects who switched from placebo or olanzapine to ALKS 3831 showed initial increases in weight, which, according to the Applicant, stabilized by approximately 4 to 6 weeks after the switch. However, during Study A305, subjects on ALKS 3831 also gained numerically more weight than olanzapine subjects.

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 at OL 12 weeks (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 50: Mean Percent Change from Baseline in Body Weight by Visit and Treatment Sequence Through Week 12 of the Extension Studies**



Source: Integrated Summary of Efficacy, Figure 38

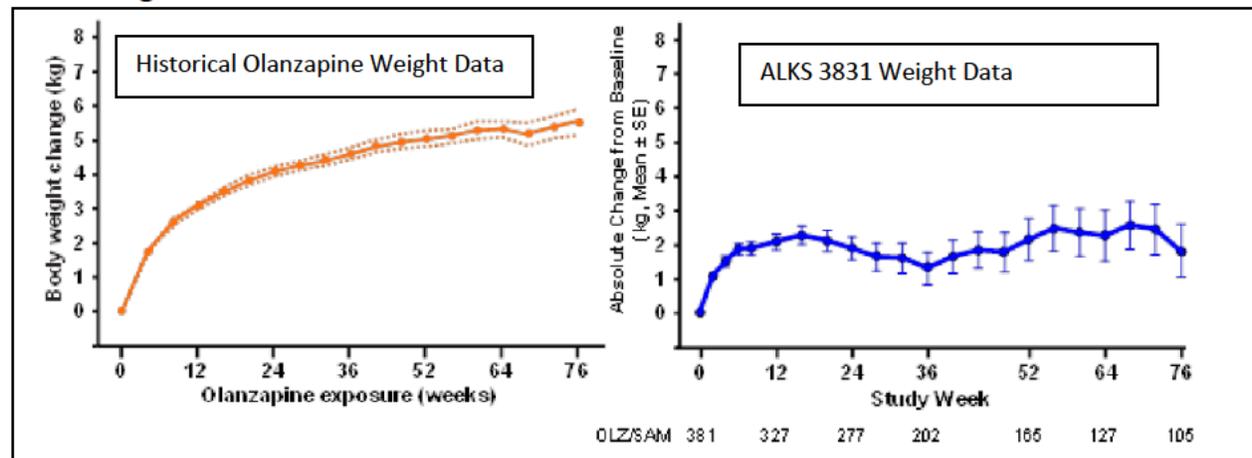
**Table 50: Mean Percent Change From Baseline in Body Weight by Visit and Treatment Sequence for Study A304 (Extension Study of A303), Selected Visits**

	ALKS 3831 during A303	Olanzapine during A303
Baseline	N=249	N=132
Mean (SD)	76.9 (13.69)	78.1 (13.68)
Week 24 (Switch to ALKS 3831)	N=177	N=132
Mean (SD)	78.9 (14.16)	82.4 (15.02)
Mean (SD) change from baseline, %	3.9 (7.72)	5.6 (7.58)
Mean (SD) change from baseline, kg	2.8 (5.61)	4.3 (5.96)
Week 28	N=127	N=128
Mean (SD)	78.7 (14.27)	83.1 (15.41)
Mean (SD) change from baseline, %	4.0 (8.16)	5.9 (8.43)
Mean (SD) change from baseline, kg	2.8 (6.01)	4.6 (6.77)
Week 36	N=120	N=113
Mean (SD)	78.8 (14.43)	83.7 (16.044)
Mean (SD) change from baseline, %	3.5 (9.01)	6.4 (9.42)
Mean (SD) change from baseline, kg	2.5 (6.74)	5.0 (7.72)

Source: Integrated Summary of Efficacy, Table 38

As discussed in Section 2.2, 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 51.

**Figure 51: Side-by-Side View of Historical Weight Results in Long-Term OLZ Studies and Long-Term Weight Results for ALKS 3831**



Source: Response to May 7, 2020, Agency Request for Information, Figure 3 (left) and Integrated Summary of Efficacy, Group 2 Figure 14.2.4.2.2 (right). Left graph based on Millen BA, et al. Weight changes over time in adults treated with the oral or depot formulations of olanzapine: A pooled analysis of 86 clinical trials. J Psychopharm. 2001;25(5):639-45.

However, this comparison is limited by missing data, the fact that 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.<sup>26</sup> According to the referenced publication that provided historical data for Figure 51, while a total of 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.<sup>27</sup> The right figure above, showing the ALKS 3831 data from the NDA, presents data starting from the first exposure of ALKS 3831 in either A303 or A304.<sup>28</sup> 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.

The effect of switching to ALKS 3831 on metabolic laboratory parameter mean changes from baseline was also included in the safety assessment. Baseline was defined as last measurement prior to ALKS 3831 dosing, and endpoint was at 52 weeks thereafter. 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. Overall, metabolic changes in comparison were mixed across studies, particularly given the inconsistent, wide range of results between the two ALKS 3831 extension groups rendering interpretation difficult.

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<sup>26</sup>Laubach JP, et al. The challenge of cross-trial comparisons using limited data. *Haematologica*. 2014;99(8):e145-6.

<sup>27</sup>Millen BA, et al. Weight changes over time in adults treated with the oral or depot formulations of olanzapine: a pooled analysis of 86 clinical trials. *J Psychopharmacol*. 2011;25(5):639-45.

<sup>28</sup>The inclusion of ALKS 3831 in long-term analyses varied depending on whether the subject was randomized to ALKS 3831 or OLZ or placebo in the respective controlled study (either A303 or A305). Baseline was defined as the last non-missing value on or before the first dose of ALKS 3831.

**Table 51: Weight and Metabolic Laboratory Parameters (Switching to Studies A304 and A306)**

	Group 1	Group 2	Zyprexa Label	CATIE study <sup>29</sup>	EUFEST study <sup>30</sup>	CAFE study <sup>31</sup>	Kinon, et al. <sup>32</sup>
Duration	52 weeks	52 weeks	>48 weeks	18 months	52 weeks	52 weeks	1 to 3 years
N	281	381	Up to 2021	120	75	42	Up to 573
Body weight (kg), mean change (SD)	2.6 (6.5)	2.1 (7.8)	5.6	4.3	13.9 (1.7)	11.1	6.3
Weight gain >7% body weight, %	30	23	64	30	86	80	52
Glucose (mg/dL), mean change (SD)	6.7 (14.3)	4.2 (18.4)	4.2	15 (2.8)	9	8.6 (1.6)	—
HbA1c (%), mean change (SD)	-0.05 (0.34)	0.07 (0.43)	—	0.41 (0.09)	—	—	—
Total cholesterol (mg/dL), mean (SD)	9.0 (33.7)	-0.2 (27.9)	5.6	9.7 (2.1)	30.9	15.7 (4.3)	—
HDL (mg/dL), mean change (SD)	1.2 (13.3)	-3.0 (14.3)	-0.2	—	-3.9 (0)	-6.5 (0.9)	—
LDL (mg/dL), mean change (SD)	10.5 (30.0)	-0.3 (26.0)	2.5	—	27.1	—	—
TG (mg/dL), mean change (SD)	23.0 (70.8)	-0.7 (69.8)	18.7	42.9 (8.4)	26.6	66.4 (12.9)	—

Source: Reviewer generated.

To augment this long-term metabolic data on mean changes from baseline, Studies A304 and A306 proportions of subjects with potentially clinically significant shifts is presented in Table 52. This comparison is significantly limited because additionally, the baseline for these data is baseline measurement at the start of the respective extension study as opposed to measurement prior to ALKS 3831 dosing. 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 and lipid shift rates when compared to historical data.

<sup>29</sup> Lieberman, J.A., et al. *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*. N Engl J Med, 2005. 353:1209-1223.

<sup>30</sup> Kahn, R.S., et al. *Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial*. Lancet, 2008. 371:1085-97. Note that this was an OL study in subjects with early illness.

<sup>31</sup> McEvoy, J.P., et al. *Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison*. Am J Psychiatry, 2007. 164:1050-60.

<sup>32</sup> Kinon, B.J., et al. *Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia*. J Clin Psychiatry, 2001. 62:92-100. Note that this was a retrospective study with some subjects receiving OL treatment.

**Table 52: Weight and Metabolic Laboratory Parameters (Studies A304 and A306)**

	Study A304	Study A306	Zyprexa Label	EUFEST study <sup>33</sup>	CAFE study <sup>34</sup>	Kinon, et al. <sup>35</sup>
Study duration	52 weeks	52 weeks	>48 weeks	52 weeks	52 weeks	1 to 3 years
N (completed /enrolled)	167/265	183/277	Up to 2021	75/104	42/133	147/573
Proportion of subjects with potentially clinically significant results (%)						
Total cholesterol < 200 mg/dL to ≥240 mg/dL		8.9	14.8	—	—	
Total cholesterol <240 mg/dL to ≥240 mg/dL	10.1	14.8				15.7
LDL <100 mg/dL to ≥160 mg/dL		5.5	7.3	—	—	—
LDL <160 mg/dL to ≥160 mg/dL	13.5	16.8				
HDL <40 mg/dL	15.3	26.6		25	48.9-50 <sup>a</sup>	—
TG <150 mg/dL to ≥200 mg/dL		15.9	32.4	—	—	—
TG <200 mg/dL to ≥200 mg/dL	16.7	24.0				
Glucose normal (<100 mg/dL) to high (≥126 mg/dL)	9.7	7.6	12.8	—	—	—
Glucose normal (<100 mg/dL) to borderline/high (≥100 mg/dL)	57	—	—	30	25.5	—
Glucose borderline (≥100 mg/dL to <126 mg/dL) to high (≥126 mg/dL)	16.2	18.8	26.0	—	—	—

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

Source: Reviewer generated.

As previously mentioned, significant factors impacting interpretability of these metabolic data from Studies ALK3831-A304 and 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.

<sup>33</sup> Kahn, R.S., et al. *Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial*. *Lancet*, 2008. 371:1085-97. Note that this was an OL study in subjects with early illness.

<sup>34</sup> McEvoy, J.P., et al. *Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison*. *Am J Psychiatry*, 2007. 164:1050-60.

<sup>35</sup> Kinon, B.J., et al. *Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia*. *J Clin Psychiatry*, 2001. 62:92-100. Note that this was a retrospective study with some subjects receiving OL treatment.

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.

### 8.2.5 Integrated Assessment of Weight Mitigation

In randomized, double-blind, and controlled periods of Studies A303 and 302, treatment with ALKS 3831 was associated with less weight gain than treatment with olanzapine alone. A summary of results related to the mitigation of weight gain and related metabolic parameters is as follows:

- In Study A303, the mean difference in weight gain between groups at Week 24 was -2.38% (95% CI=-3.88, -0.88) and in Study 302, the mean difference between groups at Week 12 ranged between -1.2% and -1.9% depending on dose. Furthermore, in the population of subjects in Study 302 that gained weight during the olanzapine lead-in week (FAS 2), the treatment difference between groups at Week 12 ranged from -1.4% to -3.7% in an apparent dose-related fashion.
- In Study A303, the proportion of subjects with weight gain of 10% or more at Week 24 was 17.8% in the ALKS 3831 group and 29.8% in the olanzapine group (odds ratio 0.50 [95% CI 0.31, 0.80]), and the proportion of subjects with weight gain of 7% or more was 27.5% in the ALKS 3831 group and 42.7% in the olanzapine group (odds ratio 0.50 [95% CI 0.33, 0.76]).
- In Study A303, the difference in waist circumference between groups (ALKS 3831 – OLZ) was -2.12 cm at Week 24. No difference in waist circumference was observed in Study 302.
- In both studies, metabolic changes (lipids and glycemic laboratory values) were generally small. In Study A303, some categorical shifts in lipids (for example, triglycerides) tended to favor ALKS 3831, whereas more subjects on ALKS 3831 had increases in fasting glucose. A suggestion of glucose increases with ALKS 3831 were also seen in Study 302 in the analysis of increases of 10 mg/dL or more from baseline. Nevertheless, glycemia-related AEs were more frequent with olanzapine and the various evaluations for insulin resistance showed mixed results.
- In Study A303, an approximately 2 mmHg difference in systolic blood pressure was observed in favor of ALKS 3831 (greater with olanzapine). No difference was observed in blood pressure in Study 302.

The clinical significance of the modest amount of weight difference in the setting of inconsistent cardiometabolic changes is uncertain. Furthermore, the interpretation of long-term data is difficult as the extension studies were open-label without an olanzapine-only control.

## 8.2.6 Other Safety Results

AE summaries for Studies A305 and A303 are as follows:

**Table 53: Adverse Events Summary (Study A305)**

	ALKS 3831 N=134 n (%)	Olanzapine N=133 n (%)	Placebo N=134 n (%)
Subjects with any AE	73 (54)	73 (55)	60 (45)
Subjects with any Adverse Events leading to death	0	1 (1)	0
Subjects with any SAE	1 (1)	1 (1)	0
Subjects with severe AE	2 (1)	2 (2)	3 (2)
Subjects with any Adverse Events leading to permanent treatment discontinuation	2 (1)	3 (2)	7 (5)

Source: Study A305 adae.xpt reviewer-coded dataset and output via JMP

**Table 54: Adverse Events Summary (Study A303)**

	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Subjects with any AE	203 (74)	227 (82)
Subjects with any Adverse Events leading to death	0	0
Subjects with any SAE	10 (4)	7 (3)
Subjects with severe AE	11 (4)	7 (3)
Subjects with any Adverse Events leading to permanent treatment discontinuation	35 (13)	28 (10)

Source: Study A303 adae.xpt reviewer-coded dataset and output via JMP

### 8.2.6.1 Deaths

Three deaths occurred in this development program, but all were unlikely related to treatment. Death narratives were reviewed. In phase 2 Study 401 which enrolled subjects with schizophrenia and alcohol use disorder, one subject randomized to ALKS 3831 treatment died secondary to Chronic Obstructive Pulmonary Disease (COPD) exacerbation and a second subject randomized to olanzapine treatment (although he also received 14 days of open-label ALKS 3831 treatment prior to randomization) died from alcohol poisoning. In phase 3 Study A305, one subject randomized to olanzapine treatment died secondary to heroin overdose.

Subject 401- (b) (6) was a 44-year-old white male with a history of schizophrenia, alcohol use disorder, insomnia, asthma, gastro-esophageal reflux disorder, mild dyskinesia, anemia and a distant history of brain trauma/injury secondary to a motor vehicle accident. The Applicant reports further history of COPD and history of tobacco use in the MedWatch report following the subject's death. He received open-label olanzapine 20 mg for 28 days then ALKS 3831 for 126 days. The subject presented to the hospital on "an unspecified date" with complaint of difficulty breathing; he was found to be suffering from a pneumothorax and was diagnosed

with an acute bronchopneumonia. He subsequently became unresponsive warranting resuscitation and mechanical ventilation. Autopsy concluded cause of death to be COPD complications and underlying hypertensive cardiovascular disease. During the study, the subject experienced an AE of weight gain.

Subject 401- (b) (6) was a 34-year-old black male with a history of schizophrenia, alcohol use disorder, hypertension, esotropia, and a distant history of polysubstance abuse. The Applicant reports further history of drug overdose with suicidal intent in the month prior to the study in the MedWatch report following the subject's death. Prior and concomitant medication included haloperidol and lisinopril. He received open-label olanzapine 10 mg for 27 days, then open-label ALKS 3831 for 14 days, then olanzapine for 85 days. The subject was reportedly drinking alcohol excessively with friends and was later found unresponsive. Interventions included emergency medical services and emergency room resuscitation and intubation followed by intensive care unit monitoring and treatment for multiple organ failure. During hospitalization the family raised concern for assault, presumably on the night of the incident. The hospital death summary listed presumed causes of death: alcohol intoxication, cardiopulmonary arrest, hyperkalemia, metabolic acidosis, acute respiratory failure, shock liver, multisystem organ failure, anoxic brain injury, and acute kidney injury. Autopsy was performed but the report was inaccessible secondary to absent immediate family or a guardian to authorize release. This subject did not report any AEs during the study.

Subject A305- (b) (6) was a 54-year-old white male with a history of schizophrenia, anxiety, insomnia, a history of right arm skin infection and graft, and sporadic methamphetamine abuse. He received olanzapine 10 mg titrated to 20 mg treatment to the end of the double-blind treatment portion of study (26 days), at which point he was deemed "stable and in good condition." The subject did report TEAEs of dizziness and weight gain. Two days following the last treatment dose, the subject was found deceased; the coroner report concluded cause of death to be "heroin intoxication."

#### **8.2.6.2 Serious Adverse Events**

Overall, 19 subjects (2%) out of 951 experienced SAEs in Studies A305 and A303. The rates of SAEs for the ALKS 3831 and olanzapine treatment arms were similar, and there were no notable trends.

##### *Study A305*

Two subjects experienced SAEs, but both were unlikely related to ALKS 3831 treatment. One subject randomized to ALKS 3831 treatment reported worsening schizophrenia on Study Day 7 and experienced catatonia on Day 9; he experienced full recovery of catatonia on Day 11. Another subject randomized to olanzapine treatment died secondary to heroin overdose, as aforementioned in the section describing deaths.

*Study A303*

There were 17 subjects (3.1%) that experienced SAEs. SAEs occurring in more than one subject were schizophrenia and drug abuse; although both of the drug abuse SAEs occurred in subjects randomized to ALKS 3831, incidence of any drug abuse TEAE was equal between both treatment groups at 1%. In a subject on ALKS 3831, a rectal hemorrhage event described as blood with wiping and clots with a mild anemia occurred in a subject with a history of hemorrhoids and recent NSAID use; additionally, colonoscopy showed helicobacter pylori gastritis. In another subject on ALKS 3831, a pleural effusion event was secondary to pneumonia.

**Table 55: Serious Adverse Events (Study A303)**

	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Any Serious TEAE	10 (4)	7 (3)
Drug Abuse	2 (1)	0
Schizophrenia	1 (<1)	3 (1)
Somnolence	1 (<1)	0
Suicidal Ideation	1 (<1)	0
Heart Rate Increased	1 (<1)	0
Infection	1 (<1)	2 (1)
Fracture	1 (<1)	0
Rectal Hemorrhage	1 (<1)	0
Pleural Effusion	1 (<1)	0
Road Traffic Accident	0	1 (<1)
Mental Status Changes	0	1 (<1)

Source: Study A303 adae.xpt reviewer-coded dataset and output via JMP

In the open-label extension Studies A306 and A304, there were few novel SAEs, none of which indicated a new trend. In Study A306, single incidents of the following SAEs were reported: viral gastroenteritis, tibial and fibular fractures, intentional overdose, and suicide attempt. In Study A304, single incidents of the following SAEs were reported: alcoholic gastritis and acute kidney injury occurring in a single subject and pulmonary embolism (PE). The PE occurred in Subject (b) (6) a 34-year-old American Indian or Alaska Native and black male with a medical history of depression and anxiety and prior medication history of exposure prophylaxis emtricitabine/tenofovir. He had received olanzapine 20 mg to completion in Study A303 then switched to ALKS 3831 20 mg for 224 days. On Day 219, the subject presented to the ER with complaint of chest pain and shortness of breath but eloped before discharge. On Day 222, he was hospitalized and treated for a PE; of note, toxicology screen was positive for methamphetamines and opiates. Two days later, he was discharged in stable condition with a

prescription for prophylactic apixaban. PE etiology was possibly dehydration (excessively hot ambient temperature) and amphetamine use but probably related to study drug. Thromboembolic events, including PE, have been reported as postmarketing events associated with olanzapine use.

In phase 2 supportive Study 302, there were few novel SAEs, none of which indicated a new trend. Single incident SAEs of arthralgia, subcutaneous abscess, and dehydration were reported in the ALKS 3831 group (all likely unrelated to study treatment) and ischemic stroke in the olanzapine group. Dehydration occurred in Subject (b) (6), a 45-year-old black male with a history of insomnia, depression, anxiety, and suicidal ideation and with concomitant medications sertraline and trazodone. He had received open-label olanzapine 5 mg for 7 days then was randomized to receive olanzapine 15 mg/samidorphan 10 mg, which he continued in the active-treatment portion of the study for a total of 169 days. On Day 188, 12 days after last treatment dose, the subject was hospitalized and treated for dehydration after walking for a prolonged period of time in excessive heat; he was recovered upon discharge the following day. The stroke occurred in Subject (b) (6), a 48-year-old black male with a concomitant history of hypertension and tobacco use and with concomitant medications atenolol and hydrochlorothiazide. He had received open-label olanzapine 5 mg for 7 days then was randomized to receive olanzapine 10 mg for 22 days. On Day 30, the subject was hospitalized and treated for a right-sided ischemic stroke then discharged to an acute rehabilitation facility. At follow-up, the event had resolved, but the subject had persistent weakness and speech impairment. This incident of stroke was deemed possibly related to treatment. Although this subject was relatively young, cerebrovascular events, including strokes, have been reported in studies of elderly patients with dementia-related psychosis.

### 8.2.6.3 Discontinuations Due to Adverse Effects

Overall, 71 subjects (7.5%) out of 951 experienced AEDCs in Studies A305 and A303. The rates of AEDCs for the ALKS 3831 and olanzapine treatment arms were similar and were less than the placebo arm; there were no notable trends.

#### *Study A305*

There were 12 subjects (3%) that experienced an AEDC; the most common AE was schizophrenia in 7 subjects: 6 were randomized to the placebo arm, and 1 to the ALKS 3831 arm.

**Table 56: Adverse Events Leading to Discontinuation (Study A305)**

	ALKS 3831 N=134 n (%)	Olanzapine N=133 n (%)	Placebo N=134 n (%)
Any AE Leading to Study Drug Discontinuation	2 (1)	3 (2)	7 (5)
Schizophrenia	1 (1)	0	6 (4)
Liver Function Test Abnormal	1 (1)	0	0
Blood Glucose Increased	0	1 (1)	0
Neutrophil Count Decreased	0	1 (1)	0
Toxicity to Various Agents	0	1 (1)	0
Seizure	0	0	1 (1)

Source: Study A305 adae.xpt reviewer-coded dataset and output via JMP

**Study A303**

There were 63 subjects (11.5%) that experienced an AEDC. The most common AEs were increased glycosylated hemoglobin, somnolence, neutrophil count decreased, weight increased, schizophrenia, and drug abuse. There were two instances of mental status change: One subject randomized to ALKS 3831, upon treatment initiation, experienced disorientation along with somnolence, nausea, and vomiting; another subject randomized to olanzapine treatment experienced decreased level of consciousness—this subject admitted to continuing his prior psychiatric medications (divalproex, mirtazapine, and paliperidone) despite study drug initiation.

**Table 57: Adverse Events Leading to Discontinuation (Study A303)**

	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Any AE Leading to Study Drug Discontinuation	35 (13)	28 (10)
Somnolence	5 (2)	2 (1)
Neutrophil Count Decreased	4 (1)	3 (1)
Weight Increased	4 (1)	2 (1)
Glycosylated Hemoglobin Increased	3 (1)	6 (2)
Schizophrenia	3 (1)	3 (1)
Drug Abuse	3 (1)	2 (1)
Liver Function Test Abnormal	2 (1)	1 (<1)
Fatigue	1 (<1)	1 (<1)
Mental Status Changes	1 (<1)	1 (<1)
Headache	1 (<1)	0
Vomiting	1 (<1)	0
Rash	1 (<1)	0
Blood Creatine Phosphokinase Increased	1 (<1)	0
Rectal Hemorrhage	1 (<1)	0

	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Blood Creatinine Increased	1 (<1)	0
Pleural Effusion	1 (<1)	0
Priapism	1 (<1)	0
Mastitis	1 (<1)	0
Blood Glucose Increased	0	2 (1)
Blood Insulin Increased	0	1 (<1)
Suicidal Ideation	0	1 (<1)
Accidental Overdose	0	1 (<1)
Dystonia	0	1 (<1)
Road Traffic Accident	0	1 (<1)

Source: Study A303 adae.xpt reviewer-coded dataset and output via JMP

In the open-label extension Studies A306 and A304, there were few novel AEDCs, none of which indicated a new trend. In Study A306, single incidents of the following AEDCs were reported: viral gastroenteritis, intentional overdose, blood insulin increased, dizziness, blood glucose increased, and suicide attempt. In Study A304, single incidents of the following AEDCs were reported: electrocardiogram change, nausea, PE (also classified as an SAE as described above), dyslipidemia, dizziness, seizure, and blood prolactin increased.

In phase 2 supportive Study 302, there were few novel AEDCs, none of which indicated a new trend. Single incident AEDCs of hypertension, anxiety, dizziness, irritability, and malaise and two incidents of suicidal ideation were reported during ALKS 3831 treatment. Single incident AEDCs of muscle spasm and ischemic stroke (also classified as an SAE as described above) were reported during olanzapine treatment.

#### 8.2.6.4 Severe Adverse Events

Overall, when looking at Applicant-rated severe AEs, there were no severe AEs that showed potential trends.

##### *Study A305*

There were eight total AEs rated as severe by the Applicant in this study, but one was a redundant AE in the same subject (anxiety).

Two anxiety AEs were rated as severe: one each in the olanzapine and placebo arms.

Three schizophrenia AEs were rated as severe: one in the ALKS 3831 arm and two in the placebo arm.

One other severe AE with ALKS 3831 was shoulder pain; one other severe AE with olanzapine was heroin intoxication (the aforementioned death).

*Study A303*

Seventeen subjects reported 21 total AEs rated as severe by the Applicant in this study, but one was a redundant AE in the same subject (white blood cell and neutrophil counts decreased). The most common severe AE was schizophrenia.

**Table 58: Severe Adverse Events (Study A303)**

	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Any Severe TEAE	11 (4)	7 (3)
Fracture	2 (1)	0
Schizophrenia	1 (<1)	2 (1)
Headache	1 (<1)	1 (<1)
Upper Respiratory Tract Infection	1 (<1)	0
Vomiting	1 (<1)	0
Neutrophil Count Decreased	1 (<1)	0
Decreased Appetite	1 (<1)	0
Blood Creatine Phosphokinase Increased	1 (<1)	0
Depression	1 (<1)	0
Priapism	1 (<1)	0
Somnolence	0	1 (<1)
Weight Increased	0	1 (<1)
Dermatitis	0	1 (<1)
Mental Status Changes	0	1 (<1)

Source: Study A303 adae.xpt reviewer-coded dataset and output via JMP

In the open-label extension Studies A306 and A304, there were few novel severe AEs, none of which indicated a new trend. In Study A306, single incidents of the following severe AEs were reported: road traffic accident and fractures, overdose, and suicide attempt. In Study A304, one severe AE of glycosuria and one of seizure were reported.

**8.2.6.5 Treatment Emergent Adverse Events and Adverse Reactions**

The most common AEs reported in pivotal Studies A305 and A303 were somnolence, weight gain, and dry mouth; only dry mouth was consistently more frequent with ALKS 3831 treatment.

The following common AEs tables include any AE with ALKS 3831 that occurred at greater than or equal to 2% incidence.

*Study A305*

There were no new safety signals in this study based upon reported AEs. Subjects in the ALKS 3831 group experienced similar rates of any TEAEs to subjects in the olanzapine group but

greater than subjects in the placebo group. Rates of SAEs and severe AEs were similar between all three groups. Subjects in the placebo group experienced higher rates of AEDCs, but rates were similarly lower in the ALKS 3831 and olanzapine groups.

ALKS 3831 AEs occurring at a rate  $\geq 5\%$  and at least double placebo included: weight increased, somnolence, dry mouth, headache, and anxiety; these AEs occurred at rates similar to olanzapine AEs except for weight increased which was greater (ALKS 3831 19% compared to olanzapine 14%). The latter is of unclear clinical significance given the relatively short duration of study.

**Table 59: Common Adverse Events (Study A305)**

	ALKS 3831 N=134 n (%)	Olanzapine N=133 n (%)	Placebo N=134 n (%)
Weight Increased	25 (19)	19 (14)	4 (3)
Somnolence	15 (11)	14 (11)	3 (2)
Dry Mouth	10 (7)	7 (5)	1 (1)
Headache	8 (6)	7 (5)	4 (3)
Anxiety	8 (6)	7 (5)	8 (6)
Upper Respiratory Tract Infection	7 (5)	2 (2)	5 (4)
Agitation	5 (4)	2 (2)	6 (4)
Musculoskeletal Pain	4 (3)	8 (6)	2 (1)
Blood Insulin Increased	4 (3)	2 (2)	1 (1)
Constipation	4 (3)	3 (2)	4 (3)
Toothache	4 (3)	1 (1)	0
Abdominal Discomfort	3 (2)	2 (2)	1 (1)
Dizziness	3 (2)	3 (2)	1 (1)
Neutrophil Count Decreased	3 (2)	1 (1)	0
Liver Function Test Abnormal	3 (2)	5 (4)	0

Source: Study A305 adae.xpt reviewer-coded dataset and output via JMP

### Study A303

There were no new safety signals in this study based upon reported AEs. Subjects in the ALKS 3831 group experienced lower rates of any TEAEs compared to subjects in the olanzapine group. Rates of SAEs, severe AEs, and AEDCs were similar between both groups.

ALKS 3831 AEs occurring at rates  $\geq 5\%$  included: somnolence, weight increased, dry mouth, increased appetite, fatigue, infection, waist circumference increased, extra dose administered, and blood creatine phosphokinase increased. Fatigue, dry mouth, and somnolence occurred with ALKS 3831 at rates greater than with olanzapine; these AEs are notable but not generally serious to warrant a safety signal. ALKS 3831 weight increased AEs occurred at a rate less than olanzapine AEs. See Section 1.1 for further weight and metabolic discussion.

**Table 60: Common Adverse Events (Study A303)**

	ALKS 3831 N=274 n (%)	Olanzapine N=276 n (%)
Somnolence	71 (26)	62 (22)
Weight Increased	68 (25)	100 (36)
Dry Mouth	35 (13)	22 (8)
Increased Appetite	32 (12)	35 (13)
Fatigue	20 (7)	11 (4)
Infection	17 (6)	15 (5)
Waist Circumference Increased	17 (6)	22 (8)
Extra Dose Administered	15 (5)	19 (7)
Blood Creatine Phosphokinase Increased	14 (5)	12 (4)
Musculoskeletal Pain	12 (4)	20 (7)
Headache	11 (4)	11 (4)
Liver Function Test Abnormal	11 (4)	11 (4)
Dizziness	9 (3)	12 (4)
Akathisia	9 (3)	4 (1)
Upper Respiratory Tract Infection	8 (3)	20 (7)
Blood Pressure Increased	8 (3)	3 (1)
Neutrophil Count Decreased	7 (3)	6 (2)
Nausea	7 (3)	8 (3)
Constipation	7 (3)	6 (2)
Abdominal Discomfort	6 (2)	3 (1)
Blood Insulin Increased	6 (2)	12 (4)
Weight Decreased	6 (2)	3 (1)
Schizophrenia	5 (2)	8 (3)
Vomiting	5 (2)	6 (2)
Dyslipidemia	5 (2)	11 (4)
Toothache	5 (2)	3 (1)
Blood Prolactin Increased	5 (2)	7 (3)
Dermatitis	5 (2)	4 (1)
Agitation	5 (2)	2 (1)

Source: Study A303 adae.xpt reviewer-coded dataset and output via JMP

**Study A306**

ALKS 3831 AEs occurring at rates  $\geq 5\%$  included: weight increased, somnolence, and upper respiratory tract infection. Note that this long-term extension study did not include a comparator arm.

**Table 61: Common Adverse Events (Study A306)**

Double-blind treatment in Study A303	ALKS 3831 N=99	Olanzapine N=90	Placebo N=88	Combined N=277
Weight Increased	18 (18)	10 (11)	9 (10)	37 (13)
Somnolence	6 (6)	10 (11)	11 (13)	27 (10)
Upper Respiratory Tract Infection	4 (4)	6 (7)	7 (8)	17 (6)
Headache	4 (4)	4 (4)	3 (3)	11 (4)
Schizophrenia	6 (6)	4 (4)	1 (1)	11 (4)
Extra Dose Administered	2 (2)	3 (3)	4 (5)	9 (3)
Musculoskeletal Pain	4 (4)	2 (2)	2 (2)	8 (3)
Infection	2 (2)	0	6 (7)	8 (3)
Anxiety	1 (1)	4 (4)	2 (2)	7 (3)
Dry Mouth	3 (3)	2 (2)	2 (2)	7 (3)
Social Stay Hospitalization	1 (1)	4 (4)	2 (2)	7 (3)
Blood Insulin Increased	3 (3)	2 (2)	1 (1)	6 (2)
Insomnia	2 (2)	2 (2)	2 (2)	6 (2)
Weight Decreased	3 (3)	3 (3)	0	6 (2)
Blood Prolactin Increased	1 (1)	2 (2)	3 (3)	6 (2)
Blood Pressure Increased	2 (2)	1 (1)	2 (2)	5 (2)

Source: Study A306 adae.xpt reviewer-coded dataset and output via JMP

**Study A304**

ALKS 3831 AEs occurring at rates  $\geq 5\%$  included: upper respiratory tract infection, weight decreased, extra dose administered, headache, musculoskeletal pain, weight increased, and infection. Note that this long-term extension study did not include a comparator arm.

**Table 62: Common Adverse Events (Study A304)**

Double-blind treatment in Study A305	ALKS 3831 N=132 n (%)	Olanzapine N=133 n (%)	Combined N=265 n (%)
Upper Respiratory Tract Infection	17 (13)	8 (6)	25 (9)
Weight Decreased	12 (9)	11 (8)	23 (9)
Extra Dose Administered	11 (8)	10 (8)	21 (8)
Headache	7 (5)	12 (9)	19 (7)
Musculoskeletal Pain	12 (9)	7 (5)	19 (7)
Weight Increased	8 (6)	8 (6)	16 (6)
Infection	7 (5)	9 (7)	16 (6)
Blood Pressure Increased	4 (3)	5 (4)	9 (3)
Somnolence	3 (2)	5 (4)	8 (3)
Blood Creatine Phosphokinase Increased	3 (2)	5 (4)	8 (3)
Nausea	3 (2)	4 (3)	7 (3)
Toothache	2 (2)	5 (4)	7 (3)
Abdominal Pain	0	6 (5)	6 (2)
Anxiety	2 (2)	3 (2)	5 (2)
Glycosylated Hemoglobin Increased	1 (1)	4 (3)	5 (2)
Schizophrenia	3 (2)	2 (2)	5 (2)
Vomiting	1 (1)	4 (3)	5 (2)
Constipation	2 (2)	3 (2)	5 (2)
Decreased Appetite	1 (1)	4 (3)	5 (2)
Diarrhea	2 (2)	3 (2)	5 (2)
Tremor	4 (3)	0	4 (2)
Dry Mouth	2 (2)	2 (2)	4 (2)
Insomnia	3 (3)	1 (1)	4 (2)
Tooth Infection	1 (1)	3 (2)	4 (2)
Blood prolactin increased	1 (1)	3 (2)	4 (2)
Increased Appetite	1 (1)	3 (2)	4 (2)
Waist Circumference Decreased	2 (2)	2 (2)	4 (2)

Source: Study A304 adae.xpt reviewer-coded dataset and output via JMP

### 8.2.6.6 Laboratory Findings

Overall, laboratory results in the studies did not show any new significant or concerning clinical or toxicity-related issues.

#### *Study A305*

#### Serum Chemistry

#### Liver Enzymes

Liver enzyme increase is a known antipsychotic class effect, and hepatotoxicity has been associated with naltrexone, an opioid antagonist with a similar mechanism of action to

samidorphan. Subjects in the ALKS 3831 group experienced mean shifts from baseline similar to the olanzapine group but greater than the placebo group.

**Table 63: Mean Change from Baseline in Liver Enzymes (Study A305)**

	ALKS 3831 N=134 Mean (SD)	Olanzapine N=133 Mean (SD)	Placebo N=134 Mean (SD)
ALT (U/L)	9.2 (24.4)	11.2 (23.0)	-0.2 (13.8)
AST (U/L)	5.5 (35.0)	5.0 (10.9)	0.8 (9.3)
ALP (U/L)	2.4 (10.9)	0.5 (14.2)	-2.0 (12.4)
GGT (U/L)	3.8 (14.5)	7.5 (14.7)	-0.9 (8.9)
LDH (U/L)	7.5 (62.9)	3.6 (23.6)	1.4 (29.6)

Source: Applicant's Clinical Study Report for ALK3831-A305, Table 27, page 88 (independently verified by reviewer)

Markedly abnormal liver enzyme results were infrequent and reported as follows: In the ALKS 3831 group, one subject (<1%) each experienced ALT and AST shifts from normal to  $\geq 3$  times the upper limit of normal; in the olanzapine group, three subjects (2.3%) experienced ALT shift from normal to  $\geq 3$  times the upper limit of normal; in the placebo group, no subjects experienced such significant shifts. No subjects met criteria for Hy's Law.

AEs during the treatment period from increased liver enzymes were reported as follows: three subjects (2%) in the ALKS 3831 treatment group compared to five (4%) in the olanzapine group and none in the placebo group. One of these subjects in the ALKS 3831 group discontinued the study drug.

Overall liver enzyme trends were similar between the ALKS 3831 and olanzapine treatment groups but abnormal relative to the placebo group.

**Prolactin**

Prolactin increase is a known antipsychotic class effect. Subjects in the ALKS 3831 group experienced mean shifts from baseline similar to the olanzapine group but greater than the placebo group.

**Table 64: Mean Change from Baseline in Prolactin Levels (Study A305)**

	ALKS 3831 N=134 Mean (SD)	Olanzapine N=133 Mean (SD)	Placebo N=134 Mean (SD)
Prolactin (ng/mL)	3.8 (22.9)	4.3 (24.2)	-8.5 (24.9)

Source: Reviewer-generated data from Study A305 adlb.xpt via JMP

Markedly abnormal prolactin results were reported as follows:

**Table 65: Abnormal Prolactin Levels (Study A305)**

	ALKS 3831 N=134 n/n subgroup <sup>a</sup> (%)	Olanzapine N=133 n/n subgroup (%)	Placebo N=134 n/n subgroup (%)
>20 ng/mL (male)	24/73 (33)	23/62 (37)	3/62 (5)
>30 ng/mL (female)	12/29 (41)	23/41 (56)	4/40 (10)

<sup>a</sup>Subjects meeting baseline criteria per shift category and with at least one postbaseline value

Source: Applicant's Clinical Study Report for ALK3831-A305, Table 14.3.4.3.1, page 832 (independently verified by reviewer)

AEs during the treatment period from increase in prolactin level included one subject (1%) in the olanzapine treatment group; this subject did not discontinue the study drug. There were no AEs related to irregular menses or decreased sexual function.

Overall prolactin level trends favored ALKS 3831 treatment over olanzapine treatment but remained markedly abnormal relative to placebo.

Lipid Profile

Lipid profile abnormalities are a known antipsychotic class effect. Subjects in the ALKS 3831 group experienced greater mean shifts from baseline than the olanzapine group across all lipid parameters, particularly for total cholesterol and triglycerides. Both ALKS 3831 and olanzapine group mean shifts were greater than placebo group shifts.

**Table 66: Mean Change from Baseline in Lipid Profiles (Study A305)**

	ALKS 3831 N=134 Mean (SD)	Olanzapine N=133 Mean (SD)	Placebo N=134 Mean (SD)
Total cholesterol (mg/dL)	15.5 (28.0)	10.9 (28.1)	3.1 (29.1)
LDL cholesterol (mg/dL)	11.6 (23.7)	9.4 (23.9)	4.0 (25.2)
HDL cholesterol (mg/dL)	-1.5 (9.1)	-0.8 (9.1)	-0.8 (10.3)
Triglycerides (mg/dL)	31.4 (67.6)	20.5 (103.7)	3.5 (41.1)

Source: Reviewer-generated data from Study A305 adlb.xpt via JMP

Shift from normal to borderline elevated total cholesterol was higher in the ALKS 3831 group compared to similar incidents in the olanzapine and placebo groups; however, rate of shift from normal to high total cholesterol was lower in the ALKS 3831 group. A subanalysis of note is a lower rate of abnormal triglyceride level ( $\geq 120$  mg/dL) in female subjects in the ALKS 3831 and placebo groups compared to the olanzapine group: 23/49 (47%), 23/51 (45%), and 30/52 (57%), respectively. Otherwise, incidence of abnormal lipid profile results was generally similar between ALKS 3831 and olanzapine groups; both groups had a greater rate of lipid

abnormalities compared to the placebo group. Laboratory results were reported as follows:

**Table 67: Abnormal Lipid Profile (Study A305)**

	ALKS 3831 N=134 n/n subgroup <sup>a</sup> (%)	Olanzapine N=133 n/n subgroup (%)	Placebo N=134 n/n subgroup (%)
Total cholesterol normal (<200) to borderline/high (≥200)	35/90 (39)	29/96 (30)	26/88 (30)
Total cholesterol normal (<200) to high (≥240)	3/90 (3)	6/96 (6)	6/88 (7)
LDL normal (<100) to borderline/high (≥100)	18/38 (47)	27/54 (50)	22/49 (45)
LDL normal (<100) to high (≥160)	1/38 (3)	1/54 (2)	2/49 (4)
HDL normal (≥40) to low (<40)	16/104 (15)	17/101 (17)	13/107 (12)
Triglycerides normal (<150) to borderline/high (≥150)	35/103 (34)	33/94 (35)	22/106 (21)
Triglycerides normal (<150) to high (≥200)	14/103 (14)	15/94 (16)	4/106 (4)

<sup>a</sup>Subjects meeting baseline criteria per shift category and with at least one postbaseline value

Source: Applicant's Clinical Study Report for ALK3831-A305, Table 30, page 92 (independently verified by reviewer)

AEs during the treatment period from abnormal lipid profile results were as follows: one subject (1%) in the ALKS 3831 treatment group compared to two (2%) in the olanzapine group and none in the placebo group. None of these subjects discontinued the study drug.

**Glycemic Parameters**

Glycemic parameter abnormalities are a known antipsychotic class effect. Subjects in the ALKS 3831 group experienced greater mean shift from baseline in fasting glucose and insulin compared to the olanzapine group, which was actually similar to shifts in the placebo group.

**Table 68: Mean Change from Baseline in Glycemic Parameters (Study A305)**

	ALKS 3831 N=134 Mean (SD)	Olanzapine N=133 Mean (SD)	Placebo N=134 Mean (SD)
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Glucose (mg/dL)	3.9 (12.3)	1.7 (20.3)	1.4 (9.9)
Insulin ( $\mu$ U/mL)	3.0 (19.8)	0.8 (22.7)	0.8 (10.3)

Source: Reviewer-generated data from Study A305 adlb.xpt via JMP

Subjects in the ALKS 3831 group also experienced a higher rate of shift to abnormally elevated glucose compared to the olanzapine group, which was actually similar to the rate in the placebo group. However, this difference was mitigated when considering only subjects with abnormally elevated glucose greater than once or at last treatment visit. HbA1c in the prediabetic range and abnormal insulin results were generally similar between ALKS 3831 and olanzapine groups; both groups had greater rates of abnormalities compared to the placebo group. HbA1c in the diabetic range was infrequent but trended higher with the olanzapine group. Laboratory results were reported as follows:

**Table 69: Abnormal Glycemic Parameters (Study A305)**

	ALKS 3831 N=134 n/n subgroup <sup>a</sup> (%)	Olanzapine N=133 n/n subgroup (%)	Placebo N=134 n/n subgroup (%)
Glucose normal (<100) to borderline/high ( $\geq$ 100) $\geq$ once	39/110 (35)	26/101 (26)	28/108 (26)
Glucose normal to borderline/high >once or at last treatment visit	28/110 (25)	22/101 (22)	17/108 (16)
Glucose normal (<100) to high ( $\geq$ 126) $\geq$ once	4/110 (4)	1/101 (1)	0/108
Glucose normal (<100) to high ( $\geq$ 126) > once	2/110 (2)	1/101 (1)	0/108
HbA1c normal (<5.7) to impaired/high ( $\geq$ 5.7)	22/91 (24)	24/103 (23)	20/103 (19)
HbA1c normal (<5.7) to high ( $\geq$ 6.5)	0/91	3/103 (3)	0/103
Insulin shift from normal to high	22/117 (19)	19/106 (18)	13/118 (11)

<sup>a</sup>Subjects meeting baseline criteria per shift category and with at least one postbaseline value

Source: Reviewer-generated data from Study A305 adlb.xpt via JMP

AEs during the treatment period from abnormal glycemic parameter results were infrequent and similar between all treatment groups as follows:

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- Glycosylated hemoglobin increased: two subjects (1%) in the ALKS 3831 group, three subjects (2%) in the olanzapine group, and none in the placebo group
- Blood glucose increased: one subject (1%) in the ALKS 3831 group, two subjects (2%) in the olanzapine group, and none in the placebo group
- Blood insulin increased: four subjects (3%) in the ALKS 3831 group, two subjects (2%) in the olanzapine group, and one subject (1%) in the placebo group
- Glycosuria: one subject (1%) in the olanzapine group and none in the ALKS 3831 and placebo groups

Only one of these subjects who was in the olanzapine group and experienced blood glucose increased discontinued the study drug.

Of note, in the long-term open-label extension Study 306, there was one reported AE of diabetes mellitus; this subject was in the olanzapine double-blind treatment group before transition to open-label ALKS 3831 and had baseline elevated glucose and insulin levels.

There was no significant mean shift from baseline or incidence of abnormal renal profile and electrolyte results, otherwise. One subject receiving placebo did experience an AE of hyperkalemia; this subject did not discontinue the study drug.

Overall mean serum chemistry results and shift tables did not show new concerning clinical trends. As an expected class effect, liver enzymes, prolactin, lipid profile, and glycemic parameter laboratory abnormalities occurred with greater frequency with ALKS 3831 and olanzapine treatment compared to placebo; this was corroborated by reported AEs. Additionally, total cholesterol, triglyceride, glucose, and insulin mean shifts from baseline were also greater with ALKS 3831 treatment compared to olanzapine; however, only rates of subjects experiencing abnormal total cholesterol and glucose levels were imbalanced in favor of olanzapine, and these differences were small.

### Hematology

Notable hematology results included a greater platelet level mean shift (in the negative) from baseline in the ALKS 3831 group compared to the olanzapine and placebo groups. However, rates of thrombocytopenia were similar in all treatment groups so mean shift from baseline is unlikely of clinical significance. Remaining hematology parameters did not demonstrate concerning trends; this includes potentially clinically significant leukocyte and neutrophil counts, which both occurred at a rate less than 2% in all treatment arms.

**Table 70: Mean Change from Baseline in Platelets (Study A305)**

	ALKS 3831 N=134 Mean (SD)	Olanzapine N=133 Mean (SD)	Placebo N=134 Mean (SD)
Platelets mean shift from baseline (SD)	-18.3 (42.5)	-3.7 (54.3)	-1.1 (50.0)
Number of subjects with platelet level <150X10 <sup>9</sup> /L (%)	3/117 (3)	4/113 (4)	3/110 (3)

Source: Reviewer-generated data from Study A305 adlb.xpt via JMP

AEs during the treatment period from abnormal hematology results were infrequent and similar between all treatment groups as follows:

- Neutrophil count decreased: three subjects (2%) in the ALKS 3831 group, one subject (1%) in the olanzapine group, and none in the placebo group
- White blood cell count increased: one subject (1%) in the ALKS 3831 group and none in the olanzapine and placebo groups
- White blood cell count decreased: one subject (1%) in the olanzapine group and none in the ALKS 3831 and placebo groups

Only one of these subjects with neutrophil count decreased in the olanzapine group discontinued the study drug.

Overall mean hematology results did not show concerning clinical trends.

#### Urinalysis

Overall urinalysis results showed no major concerning clinical trends.

#### *Study A303*

##### Serum Chemistry

##### Liver Enzymes

Liver enzyme increase is a known antipsychotic class effect, and hepatotoxicity has been associated with naltrexone, an opioid antagonist with a similar mechanism of action to samidorphan. Subjects in the ALKS 3831 group experienced mean shifts from baseline similar to the olanzapine group. Markedly abnormal liver enzyme results were infrequent and similar between the treatment groups as follows:

- ALT shift from normal to  $\geq 3$  times the upper limit of normal: nine subjects (3.4%) in the ALKS 3831 group and nine subjects (3.3%) in the olanzapine group

- AST shift from normal to  $\geq 3$  times the upper limit of normal: six subjects (2.3%) in the ALKS 3831 group and eleven subjects (4.0%) in the olanzapine group
- Total bilirubin shift from normal to  $\geq 2$  times the upper limit of normal: one subject (0.4%) in the ALKS 3831 group and three subjects (1.1%) in the olanzapine group

No subjects met criteria for Hy's Law.

AEs during the treatment period from abnormal liver function test results were similar between both treatment groups: 11 subjects (4%) in the ALKS 3831 group and 12 subjects (4%) in the olanzapine group. Three of these discontinued the study drug: two subjects (1%) in the ALKS 3831 group and one (<1%) in the olanzapine group.

Overall liver enzyme trends were similar between the ALKS 3831 and olanzapine treatment groups.

#### Creatine Kinase (CK)

CK mean shifts from baseline ranged broadly both at baseline and throughout treatment but were ultimately not significantly different between the two treatment groups. Any subjects with PCS abnormal CK results ( $\geq 3$  times the upper limit of normal) were also similar between the two groups and were reported as: ALKS 3831 39/247 (15.8%) and olanzapine 45/268 (16.8%). Upon further investigation, however, when analyzing subjects with baseline normal CK values shifting to PCS abnormal CK values, incidence was mitigated: 10/153 subjects (7%) on ALKS 3831 and 12/172 subjects (7%) on olanzapine. Further all but one of these subjects demonstrated a PCS abnormal CK result once only, and all but one subject experienced subsequent downtrend.

AEs during the treatment period from increase in CK results were also similar and included fourteen subjects (5%) in the ALKS 3831 group and twelve subjects (4%) in the olanzapine group. One subject in the ALKS 3831 group discontinued the study drug.

For both active treatment groups, overall CK level trends were similarly broad ranging and elevated, but sustained PCS abnormalities were lower— Shifts are of unlikely clinical significance.

#### Prolactin

Prolactin increase is a known antipsychotic class effect; mean shifts from baseline were less in females in the ALKS 3831 group as follows:

**Table 71: Mean Change from Baseline in Prolactin (Study A303)**

	ALKS 3831 N=274 Mean (SD)	Olanzapine N=276 Mean (SD)
Males (ng/mL)	1.25 (8.398)	0.62 (10.216)
Females (ng/mL)	-8.46 (43.432)	3.51 (18.931)

Source: Applicant's Clinical Study Report for ALK3831-A303, Table 47, page 136 (independently verified by reviewer)

Markedly abnormal prolactin results were reported as follows:

**Table 72: Abnormal Prolactin Levels (Study A303)**

	ALKS 3831 N=274 n/n subgroup <sup>a</sup> (%)	Olanzapine N=276 n/n subgroup (%)
>20 ng/mL (male)	39/173 (22.5)	51/179 (28.5)
>30 ng/mL (female)	23/70 (32.9)	25/60 (41.7)

<sup>a</sup>Subjects meeting baseline criteria per shift category and with at least one postbaseline value

Source: Applicant's Clinical Study Report for ALK3831-A303, Table 14.3.4.3.1, page 1581 (independently verified by reviewer)

AEs during the treatment period from increase in prolactin results were infrequent and similar between the two treatment groups: five subjects (2%) in the ALKS 3831 group and seven subjects (3%) in the olanzapine group. Additionally, two subjects (1%) in the ALKS 3831 group reported AEs of abnormal menses (one subject reported amenorrhea and menorrhagia and another reported metrorrhagia), and four subjects (1%) in the olanzapine group reported AEs of decreased sexual function. All but one of these subjects also had elevated prolactin levels although one of the subjects had elevation at baseline, as well. None of these subjects discontinued the study drug.

Overall prolactin level trends were notably elevated but favored ALKS 3831 treatment over olanzapine treatment.

#### Lipid Profile

See Section 1.1 for a detailed discussion of lipid profile findings for Study A303.

#### Glycemic Parameters

See Section 1.1 for a detailed discussion of lipid profile findings for Study A303.

#### Other Serum Chemistry

Significant numbers of subjects in both the ALKS 3831 and olanzapine groups demonstrated bicarbonate levels below the normative range (<22 mmol/L): 98 subjects (36%) and 114 subjects (41%), respectively. However, the abnormal result was mild ( $\geq 19$  mmol/L) in the

majority of cases and, therefore, unlikely of clinical significance. Remaining renal profile and electrolyte mean shifts from baseline or incidence of abnormal results were not significant. AEs during the treatment period from other abnormal biochemistry profile results were elevated creatinine as follows: one subject (<1%) in the ALKS 3831 treatment group compared to two (1%) in the olanzapine group. The subject in the ALKS 3831 group discontinued the study drug.

Overall mean serum chemistry results and shift tables did not show new major concerning clinical trends. Abnormal CK and bicarbonate levels were seen similarly in both treatment groups but are unlikely of clinical significance. As an expected class effect, liver enzymes, prolactin, lipid profile, and glycemic parameter laboratory abnormalities occurred with relatively high frequency with ALKS 3831 and olanzapine treatment; this was corroborated by reported AEs.

#### Hematology

Neutropenia, leukopenia, and agranulocytosis are known antipsychotic class effects. Rates of abnormalities favored ALKS 3831 slightly although the differences were small and likely not clinically significant: absolute neutrophils  $<1.5 \times 10^3/\mu\text{L}$  and leukocytes  $\leq 2.8 \times 10^3/\mu\text{L}$  in the ALKS 3831 group occurred in 16/262 subjects (6.1%) and 6/265 subjects (2.3%), respectively, compared to the olanzapine group: 25/269 subjects (9.3%) and 10/272 subjects (3.7%), respectively. Female hematocrit  $\leq 32\%$  and male hematocrit  $\leq 37\%$  occurred in the ALKS 3831 group in 1/78 subjects (1.3%) and 7/185 subjects (3.8%), respectively, compared to the olanzapine group: 3/69 subjects (4.3%) and 10/202 subjects (5%), respectively.

AEs during the treatment period from abnormal hematology results were infrequent and similar between all treatment groups as follows:

- Hemoglobin decreased: four subjects (1%) in the ALKS 3831 group and one subject (<1%) in the olanzapine group
- Neutrophil count decreased: seven subjects (3%) in the ALKS 3831 group and six subjects (2%) in the olanzapine group
- White blood cell count decreased: three subjects (1%) in the ALKS 3831 group and two subjects (1%) in the olanzapine group
- White blood cell count increased: one subject (<1%) in the olanzapine group and none in the ALKS 3831 group
- Platelet count decreased: one subject each (<1%) in both treatment groups
- Thrombocytosis: one subject (<1%) in the ALKS 3831 group and none in the olanzapine group

Seven of these subjects with neutrophil count decreased discontinued the study drug: four in the ALKS 3831 group and three in the olanzapine group.

Overall hematology parameters did not demonstrate new concerning trends.

#### Urinalysis

AEs during the treatment period from abnormal urinalysis results were as follows: three subjects (1%) in the ALKS 3831 group compared to two (1%) in the olanzapine group. None of the subjects discontinued study drug.

Overall urinalysis results and AEs did not demonstrate concerning trends.

#### **8.2.6.7 Vital Signs**

There were no consistent trends between the two pivotal studies although orthostatic hypotension is a known antipsychotic class effect.

#### *Study A305*

##### Cardiovascular/Respiratory

Mean shifts in blood pressure, heart rate, and respiratory rate were similar in all treatment groups. Rates of orthostatic hypotension were also similar in treatment groups and were all less than 2%. Rates of potentially clinically significant standing heart rate ( $\geq 120$  bpm and increase  $\geq 15$  bpm) was slightly imbalanced with greater rates in the ALKS 3831 group (5/134 subjects (4%) compared to the olanzapine and placebo groups (1/133 subjects and 1/134 subjects, respectively (both 1%). Similarly with postural tachycardia: ALKS 3831 group 9/132 subjects (6.8%) compared to the olanzapine and placebo groups both 6/133 subjects (4.5%). Changes in supine heart rate were unremarkable. The differences in standing heart rate and postural tachycardia were small and, therefore, likely not clinically significant.

AEs during the treatment period from vital sign changes were infrequent and similar between treatment groups as follows:

- Blood pressure decreased: one subject (1%) in the ALKS 3831 group and none in the olanzapine and placebo groups
- Blood pressure increased: one subject (1%) in the ALKS 3831 group, two subjects (2%) in the olanzapine group, and none in the placebo group
- Heart rate increased: one subject each (1%) in all three groups
- There were no reports of postural orthostatic tachycardia

None of these subjects discontinued the study drug.

There was a slightly greater incidence of postural/standing heart rate in the ALKS 3831 group that is of unlikely clinical significance; otherwise, these results do not show concerning clinical trends.

#### Height/Weight/BMI

Weight showed mean increases from baseline on both active treatments compared to placebo. Mean changes from baseline are as follows: ALKS 3831 3.02 kg (SD 3.564), olanzapine 2.38 kg (3.653), and placebo 0.24 kg (2.757). This is supported by proportion of subjects with clinically significant weight gain of  $\geq 7\%$  from baseline: ALKS 3831 33/128 subjects (25.8%), olanzapine 25/128 subjects (19.5%), and placebo 6/129 subjects (4.7%). Of note, baseline weight was imbalanced potentially impacting weight gain differences: ALKS 3831 mean weight was 77.86 kg (SD 15.426) with range 44.0 to 128.2 kg, olanzapine was 82.24 kg (SD 19.309) ranging from 50.0 to 141.4 kg, and placebo was 76.64 kg (SD 15.915) ranging from 44.4 to 113.9 kg.

There were 25 subjects (19%) in the ALKS 3831 group, 19 (14%) in the olanzapine group, and 4 (3%) in the placebo group who reported weight increase AEs. One subject (1%) each in the olanzapine and placebo groups reported weight decrease AEs. None of these subjects discontinued the study drug.

Overall, these results show a signal for markedly abnormal weight gain in the ALKS 3831 and olanzapine treatment arms compared to placebo with ALKS 3831 subjects experiencing greatest gain. However, these results are confounded because subjects in the olanzapine group had higher baseline weight, and this short-term study was not designed to evaluate weight gain.

#### *Study A303:*

##### Cardiovascular/Respiratory

Mean shifts in heart rate and respiratory rate and proportion of subjects with potentially clinically significant blood pressure and respiratory rate were similar in both treatment groups. Rates of potentially clinically significant supine heart rate ( $\geq 120$  bpm and increase  $\geq 15$  bpm) was slightly higher in the ALKS 3831 group (10/264 subjects (3.8%) compared to the olanzapine group (1/273 subjects (<1%). Changes in standing heart rate were unremarkable. The difference in changes in supine heart rate was small and, therefore, likely not clinically significant. See Section 1.1 for a detailed discussion of BP findings in Study A303.

Orthostatic hypotension is a known antipsychotic class effect. Rates of orthostatic hypotension were also slightly higher in the ALKS 3831 group (10/270 subjects (3.7%) compared to the olanzapine group (1/273 subjects (<1%). However, the difference was small, and, for context, the Zyprexa PI lists an orthostatic hypotension rate of 20%, and the CATIE study a rate of 9%. Therefore, this imbalance is unlikely clinically significant.

AEs during the treatment period from vital sign changes were infrequent and similar between both treatment groups as follows:

- Blood pressure increased: eight subjects (3%) in the ALKS 3831 group and three subjects (1%) in the olanzapine group
- Postural orthostatic tachycardia syndrome: three subjects (1%) in both the ALKS 3831 and olanzapine groups
- Heart rate increased: two subjects (1%) in the ALKS 3831 group and four subjects (1%) in the olanzapine group; for one of these subjects in the ALKS 3831 group, the AE was classified as a SAE
- There were no reports of orthostatic hypotension.

None of these subjects discontinued the study drug.

Section 8.2.3 discusses small benefit in supine SBP shift at final treatment visit for ALKS 3831 compared to olanzapine. There was a slightly greater incidence of supine heart rate in the ALKS 3831 group that is of unlikely clinical significance. Additionally, these results show a signal, albeit small, for abnormal orthostatic hypotension in the ALKS 3831 arm compared to olanzapine. However, orthostatic hypotension is a known effect with atypical antipsychotic class drugs, and rates in this study are low relative to historical rates. Overall, these results do not show concerning new clinical trends.

#### Height/Weight/BMI

Refer to Section 1.1 for detailed discussion of data from Study A303 regarding weight gain mitigation effects.

#### **8.2.6.8 Electrocardiograms (ECGs)**

No major ECG trends for ALKS 3831 were observed; varying small increased heart rate trends on ALKS 3831 observed in the vital sign investigations were not substantiated by these ECG results. The data tables in this section were reviewer-generated on JMP via adeg.xpt datasets for each study or copied from the Applicant's Clinical Study Reports.

#### *Study A305*

Shift tables showed heart rate trends with olanzapine treatment to be greater than with ALKS 3831 treatment, which were greater than with placebo, and PR trends with ALKS 3831 treatment greater than with olanzapine and placebo treatments. However, these differences were small and unlikely of clinical significance.

**Table 73: Mean Changes from Baseline in ECG Parameters (Study A305)**

	ALKS 3831 (N=134)	Olanzapine (N=133)	Placebo (N=134)
<b>Heart Rate (bpm)</b>			
Mean change on Day 29 from baseline (SD)	1.8 (12.81)	3.1 (13.08)	0.5 (13.09)
<b>PR Interval (msec)</b>			
Mean change on Day 29 from baseline (SD)	3.8 (11.81)	-0.1 (15.77)	0.9 (16.52)

Source: Applicant's Clinical Study Report for ALK3831-A305, Table 36, page 99 (independently verified by reviewer)

For further reassurance, there was only one subject (1%) in the olanzapine group with a HR  $\geq 120$  bpm, and there were only two subjects (one in the olanzapine group and one in the placebo group, both 1%) who had shift from normal to elevated PR interval ( $\geq 210$  ms). Remaining ECG parameter trends were unremarkable.

No ECG-related AEs were reported during the treatment period. However, there was one AE of angina pectoris in the olanzapine group, which was categorized as not serious, mild, and definitely not related. The subject recovered and continued the study. Further details were not included in the CSR.

#### QT Interval

Mean QTcF and QTcB changes from baseline showed minor differences between ALKS 3831 and olanzapine compared to placebo treatment arms as follows:

- QTcB interval: ALKS 3831 5.7 msec (SD 17.98), olanzapine 4.9 msec (21.24), and placebo -0.2 msec (19.16)
- QTcF interval: ALKS 3831 3.8 msec (SD 15.31), olanzapine 1.8 msec (15.39), and placebo -0.4 msec (14.68)

Proportion of subjects with markedly abnormal QTcB and QTcF parameters were similar between the three treatment arms:

- QTcB  $>450$  msec but  $\leq 480$  msec occurred in 14/127 subjects (11.0%) on ALKS 3831, 14/121 subjects (11.6%) on olanzapine, and 16/124 subjects (12.9%) on placebo.
- QTcB  $>480$  msec occurred in only two subjects—one each in the olanzapine and placebo groups (1% each).
- QTcF  $>450$  msec but  $\leq 480$  msec were  $\leq 3\%$  in all three treatment groups: 2/132 subjects on ALKS 3831, 4/131 subjects on olanzapine, and 2/133 subjects on placebo.
- No subjects demonstrated QTcF  $> 480$  msec.

- No subjects exceeded QTc intervals of 500 msec.

No subjects had AEs during the treatment period for electrocardiogram QT prolonged.

Overall, there were small shifts with both active treatment groups compared to placebo but no clinically significant drug-related trends in QTc prolongation in this study.

Overall, ECG results do not show clinically significant trends consistent with a new safety signal for ALKS 3831.

#### *Study A303*

RR shift was greater with ALKS 3831 treatment than olanzapine treatment, but standard deviations were broad. This shift was small, and proportions of subjects with elevated RR interval were similar. Therefore, this finding is unlikely clinically significant.

**Table 74: Mean Changes from Baseline in ECG Parameters (Study A303)**

	ALKS 3831 (N=274)	Olanzapine (N=276)
Change in RR interval (msec) from baseline, mean (SD)	7.7 (140.1)	-31.8 (156.2)
Subjects with RR interval >120 msec, n (%)	15 (5)	7 (3)

Source: Applicant's Clinical Study Report for ALK3831-A303, Table 61, page 151 (independently verified by reviewer) and reviewer-generated data from Study A305 adlb.xpt via JMP

Remaining ECG parameter trends, including heart rate, were unremarkable.

One AE of cardiac flutter in the olanzapine group was categorized as not serious, mild, and probably not related, but further details were not included in the CSR. The subject recovered and did not discontinue study drug.

#### QT Interval

Mean QTcB and QTcF shifts from baseline were unremarkable for both treatment arms: <3 msec across all QT parameters. Proportion of subjects with markedly abnormal QTcB and QTcF parameters were similar between both treatment arms:

- QTcB >450 msec but ≤500 msec occurred in 19/243 subjects (7.8%) on ALKS 3831 and 15/238 subjects (6.3%) on olanzapine.
- QTcB >500 msec occurred in 1/243 subjects (<1%) on ALKS 3831 and 1/238 subjects (<1%) on olanzapine.
- QTcF >450 msec but ≤500 msec occurred in 4/250 subjects (1.6%) on ALKS 3831 and 1/244 subjects (<1%) on olanzapine.

- QTcF >500 msec occurred in 1/250 subjects (<1%) in the ALKS 3831 group and 1/244 subjects (<1%) in the olanzapine group.

One AE of ECG change in the ALKS 3831 group was categorized as not serious, mild, and definitely not related, but further details were not included in the CSR. Upon further investigation, it appears this subject had a slightly elevated QTcB (460 msec) at baseline (unclear if before or after study drug administration) that normalized on follow-up 5 days later. The subject recovered and did not discontinue study drug.

There were no drug-related trends for QTc prolongation in this study.

#### *ECG Summary*

Overall, ECG results do not show clinically significant trends consistent with a new safety signal. QTc intervals on ALKS 3831 and olanzapine showed minor changes compared to placebo in one pivotal trial, but proportions of subjects with abnormal results were unremarkable. Two subjects exceeded QTc intervals on either QTcB or QTcF of 500 msec in the studies: one each in the ALKS 3831 and olanzapine groups. The dedicated QTc study also showed no major changes or concerns at ALKS 3831 doses ranging from 10 mg/10 mg to 30 mg/30 mg. The QT IRT reviewer did not note concern about the QT study design and data.

#### **8.2.6.9 Immunogenicity**

Rates of potential hypersensitivity-related AEs were similar in all treatment arms. In Study A303, there was one study discontinuation because of rash. There were no major hematologic findings with respect to immune reaction mediators, but hypersensitivity reactions may still occur.

##### *Study A305*

There were no subjects who had possible hypersensitivity AEs reported. However, of note, in the long-term extension Study A306, one subject experienced skin exfoliation described as “bilateral hand skin peeling.” This occurred on Study Day 357, was classified as mild and probably not related to treatment, and resolved after 13 days. Other reported AEs by the same subject included sedation, weight increased, and upper respiratory tract infection.

##### *Study A303*

There were six subjects who had possible hypersensitivity AEs reported: four (1%) were on ALKS 3831 (three with rash and one with allergic dermatitis) and two (1%) were on olanzapine (one with rash and one with lip swelling). One subject developed a rash on his neck and chest after receiving ALKS 3831 over two days so discontinued treatment; the rash was treated with diphenhydramine as needed and resolved 2 days later. The subject did not report any other TEAEs. Timing of the rashes and lip swelling varied in the remaining cases (anywhere from Day 3 to Day 25). No other hypersensitivity AEs were noted in this study.

## 8.2.7 Analysis of Submission-Specific Safety Issues

### 8.2.7.1 Extrapyramidal Symptoms (EPS)

EPS is a known antipsychotic class effect. Overall, EPS incidence rates in subjects on ALKS 3831 are generally similar to other antipsychotic medications.

#### *Study A305*

Mean EPS scale changes from baseline were not significant for all three treatment groups: AIMS changes from baseline were  $\leq 0.3$ ; BARS changes from baseline were  $\leq 0.1$ ; SAS changes from baseline were also  $\leq 0.3$ . Fifty-five subjects demonstrated EPS symptoms during the study as assessed by AIMS, BARS, and SAS: 15 (11.2%) on ALKS 3831, 13 (9.8%) on olanzapine, and 27 (20.1%) on placebo. The higher rate of EPS in the placebo group was largely driven by a greater frequency in Parkinsonism symptoms—the reason for this is unclear, but the Applicant hypothesizes that this may have been secondary to subjects tapering off of prior antipsychotics.

EPS AEs were infrequent and similar between all treatment groups. EPS-associated preferred terms are as follows:

- Akathisia: no subjects in the ALKS 3831 group, four subjects (3%) in the olanzapine group, and one subject (1%) in the placebo group
- Restlessness: no subjects in the ALKS 3831 and placebo groups and one subject (1%) in the olanzapine group
- Muscle spasms: one subject (1%) in the ALKS 3831 group and no subjects in the olanzapine and placebo groups
- Bradykinesia: one subject (1%) in the ALKS 3831 group and no subjects in the olanzapine and placebo groups
- Tremor: one subject (1%) in both the ALKS 3831 and olanzapine groups and no subject in the placebo group
- Extrapyramidal disorder: no subjects in the ALKS 3831 and placebo groups and two subjects (2%) in the olanzapine group
- Parkinsonism: no subjects in the ALKS 3831 and placebo groups and one subject (1%) in the olanzapine group

There were no study discontinuations due to EPS.

Overall, no significant drug-related trends related to EPS were noted in this study

*Study A303*

Mean EPS scale changes from baseline were not significant for both treatment groups (<0.1). Thirty-five subjects demonstrated EPS symptoms during the study as assessed by AIMS, BARS, and SAS with similar rates between treatment groups: 20 subjects (7.3%) on ALKS 3831 and 15 subjects (5.4%) on olanzapine.

EPS AEs were infrequent and similar between all treatment groups. EPS-associated preferred terms are as follows:

- Akathisia: nine subjects (3%) in the ALKS 3831 group and four subjects (1%) in the olanzapine group—This difference is small, and, for context, listed rates of akathisia in the Zyprexa PI range from 3 to 11%, which is greater than that seen with olanzapine in this study and consistent with the rate seen with ALKS 3831 in this study. Therefore, this difference is unlikely of clinical significance.
- Restlessness: one subject (<1%) in the ALKS 3831 group and six subjects (2%) in the olanzapine group
- Muscle spasms: three subjects (1%) in the ALKS 3831 group and one subject (<1%) in the olanzapine group
- Muscle tightness: one subject (<1%) in the ALKS 3831 group and no subjects in the olanzapine group
- Dyskinesia: three subjects (1%) in the ALKS 3831 group and two subjects (1%) in the olanzapine group
- Tremor: four subjects (1%) in the ALKS 3831 group and three subjects (1%) in the olanzapine group
- Extrapyrarnidal disorder: two subjects (1%) in the ALKS 3831 group and one subject (<1%) in the olanzapine group
- Dystonia: two subjects (1%) in both treatment groups

There was one study discontinuation due to dystonia in a subject on olanzapine.

Overall, no significant drug-related trends related to EPS were noted in this study

### 8.2.7.2 Suicidal Ideation and Behavior (SI/B)

Schizophrenia and bipolar disorder are inherent risks for suicidality. Overall, no SI/B signals were evident, either from AE reporting or from C-SSRS monitoring, rather the trends slightly favored ALKS 3831. There were no subjects with suicide attempt reported in the pivotal trials, but there was one attempt in a long-term extension trial that was unlikely related to study drug.

#### *Study A305*

Five subjects reported suicidal ideation during the study on the C-SSRS: none on ALKS 3831, two (1.5%) on olanzapine, and three (2.2%) on placebo.

Two subjects reported suicidal ideation AEs: none on ALKS 3831 and olanzapine and two (1%) on placebo. There were no discontinuations due to suicidal ideation in this study.

No suicidal behavior events occurred in this study.

Overall, no significant drug-related trends related to SI/B were noted in this study

#### *Study A303*

Forty-two subjects reported suicidal ideation and one reported preparatory suicidal behavior during the study on the C-SSRS with lower rates in the ALKS 3831 group (15 subjects, 5.5%) compared to the olanzapine group (28 subjects, 10.1%).

Four subjects reported suicidal ideation AEs: two subjects each (1%) in both treatment groups. There was one subject who discontinued the study due to suicidal ideation; the subject was in the olanzapine group.

Of note, there was one AE of passive homicidal ideation in a subject taking ALKS 3831; he was evaluated and discharged from the emergency room. The Applicant classified the AE as resolved, non-serious, and not related to treatment discontinuation, but the subject did discontinue treatment prematurely within 1 week (last treatment dose 3 days later and EOT visit 5 days later). This subject did not report any other AEs.

No suicidal behavior events occurred in this study.

Overall, no significant drug-related trends related to SI/B were noted in this study.

#### *Studies A304 and A306*

There was one suicide attempt in Study A306: Subject (b) (6) was a 36-year-old female with schizophrenia and right leg shortening and a history of congenital dislocation and surgery of hip, viral hepatitis, tibia fracture, and obesity. She received olanzapine in Study A305 then

initiated ALKS 3831 for 259 days in the open-label extension study. Following family conflict, the subject impulsively ingested 12 tablets of ALKS 3831 10 mg with suicidal intent; she was found in a “soporific state” and admitted to the intensive care unit of a psychiatric hospital then the general psychiatric unit. Upon discharge 30 days later, the subject was “in satisfactory mental and general medical condition,” but she did discontinue the study. PANSS scores ranged from 59 to 77 throughout the study (last score on Study Day 253 was 59), and her CGI-S scores were consistently 3 (mildly ill) until the last score obtained on Day 253 of 2 (borderline mentally ill). Other reported AEs for this subject were somnolence (reported on Day 9), insomnia (Day 179), extremity pain (Day 110), and dry mouth.

### 8.2.7.3 ALKS 3831 Abuse Potential and Withdrawal

No signals emerged from AEs evaluating for abuse potential—except for somnolence, rates of non-specific symptoms were similar between the ALKS 3831 and olanzapine groups, which were both higher than the placebo group:

- In Study A305, somnolence occurred in 15 subjects (11%) in the ALKS 3831 group, 14 subjects (11%) in the olanzapine group, and 3 subjects (2%) in the placebo group.
- In Study A305, dizziness occurred in 3 subjects (2%) in the ALKS 3831 group, 3 subjects (2%) in the olanzapine group, and 1 subject (1%) in the placebo group.
- In Study A303, somnolence occurred in 71 subjects (26%) in the ALKS 3831 group and 62 subjects (22%) in the olanzapine group.
- In Study A303, dizziness occurred in 9 subjects (3%) in the ALKS 3831 group and 12 subjects (4%) in the olanzapine group.
- There were no reports of euphoria.

Rates of substance use AEs were similar for ALKS 3831 and olanzapine groups. In Study A305, no AEs of drug abuse were reported, but there was a lethal heroin overdose event in a subject on olanzapine that was probably unrelated to treatment (see Section 8.2.3 for details). In Study A303, AEs during the treatment period were infrequent as follows:

- Extra dose administered: 15 subjects (5%) in the ALKS 3831 group and 19 subjects (7%) in the olanzapine group. One of these subjects in the olanzapine group discontinued study drug.
- Drug abuse: three subjects (1%) in the ALKS 3831 group and two subjects (1%) in the olanzapine group. All of these subjects discontinued study drug.

Drug abuse was reported in one subject in the long-term, open-label studies. Additionally, an overdose of note occurred in Study A307, which is ongoing, so data remains blinded: A subject ingested six tablets of study drug along with diphenhydramine and benzodiazepines “to get high.” The subject was admitted soporous and was intubated; after discontinuation of propofol, she experienced presumed withdrawal seizures. She recovered and was discharged 3 days later and discontinued study treatment. This event is difficult to assess secondary to continued data blinding and polysubstance overdose.

The Applicant assessed for study drug diversion by closely monitoring pill counts; adherence was high in both pivotal trials (mean 99.9% (SD 0.95) in Study A305 and 96.2% (SD 9.18) in Study A303). Thirty-four potential diversion reports were made across the ALKS 3831 development program, but none were deemed actual diversions: Fifteen were subjects who discontinued and were lost to follow-up, 8 were stolen or taken from the subject, 9 were lost, and 2 were discarded in error.

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 non-specific symptoms (nausea, depression, insomnia, tachycardia, tremor, vomiting, agitation, and headache) were unremarkable (all less than 1%).

Overall, no drug-related trends were evident from potential abuse and withdrawal symptoms that occurred during these trials.

#### **8.2.7.4 Precipitated Opioid Withdrawal, Inadequate Analgesia, and Opioid Overdose**

Given the opioid-antagonist action of samidorphan, there are safety concerns for precipitating opioid withdrawal in patients who are physically dependent on opioids as well as ineffective analgesia with concomitant opioid use. The latter could potentially result in overdose in attempting to achieve breakthrough analgesia, particularly if samidorphan’s opioid antagonist effects fluctuate during therapy or as the antagonist effect wanes following discontinuation of the drug. 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 non-dependent 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 test result at Screening. He experienced symptoms of withdrawal 2 minutes after administration of samidorphan 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. There was no AE pattern in Studies A303 or A305 that may have represented opioid withdrawal symptoms (consistent with the exclusion of people with opioid use).

Regarding concomitant medications, 18 subjects were exposed to opioids while receiving ALKS 3831. Of these, two were exposed to opioids for more than a short-term duration (13 and 37 days) for significant injuries (skeletal fractures secondary to motor vehicle accidents). 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, it is unknown if the subjects took a higher dose of opioids while on ALKS 3831 than they would have otherwise. Based upon the non-rigorous means of obtaining this information as general query of concomitant medications and the small number of subjects with reported opioid exposure, this data should be interpreted cautiously. Additionally, noteworthy, in Study A308, a subject was hospitalized for an accidental oxycodone overdose leading to discontinuation of study drug: she reported ingesting four tablets of acetaminophen, but presentation and drug testing confirmed presence of oxycodone and absence of acetaminophen.

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 Studies A303 and 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 included blood pressure increased, dry mouth, extra dose administered, increased appetite, lethargy, toothache, upper respiratory tract infection, waist circumference increased, and weight increased.

#### *Additional Considerations Based on Epidemiologic Literature*

(See the separate Office of Surveillance and Epidemiology Review for further details and references.) Overall, although there are no new safety signals with ALKS 3831, epidemiological data provides some cautionary context for the samidorphan component that bears consideration as part of the overall benefit-risk assessment.

Although chronic use of opioids and opioid dependence are proposed contraindications for ALKS 3831, 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.<sup>36</sup> 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.<sup>37</sup> 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.<sup>38</sup> 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.<sup>39,40</sup> Additionally, a study of patients with bipolar disorder receiving care at a Veterans clinic reported the prevalence of opioid use disorder at 2.7%.<sup>41</sup> Considering the estimated prevalence of nonmedical opioid use (3.6%) or opioid use disorder (0.7%) in the general U.S. population,<sup>42</sup>

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<sup>36</sup>Birgenheir DG, et al. *Pain conditions among veterans with schizophrenia or bipolar disorder*. Gen Hosp Psychiatry. 2013;35(5):480-4.

<sup>37</sup>Owen-Smith A, et al. *Chronic pain diagnoses and opioid dispensings among insured individuals with serious mental illness*. BMC Psychiatry. 2020;20(1):40.

<sup>38</sup> Martins SS et al. Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: Longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. Psychol Med. 2012;42(6):1261-72.

<sup>39</sup>Martins SS et al. Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: Longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. Psychol Med. 2012;42(6):1261-72.

<sup>40</sup>Saha T.D., et al. Nonmedical prescription opioid use and DSM-5 Nonmedical Prescription Opioid Use Disorder in the United States. Journal of Clinical Psychiatry, 2016. 77(6): p.772-780.

<sup>41</sup> Bauer et al., *Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder*. J. Affect Disord, 2005. 85(3):p. 301-315.

<sup>42</sup>Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States. Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data>.

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 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. 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,<sup>43,44</sup> however, more recent, smaller studies suggest that individuals with schizophrenia and substance use disorders may prefer other drugs to opioids.

A 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. These cases also 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

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<sup>43</sup> Regier, DA et al., Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*, 1990. 264(19): p.2511-8.

<sup>44</sup> Martins, SS et al., Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the US population. *Drug Alcohol Depend*, 2011. 119(1-2): p. 28-36.

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, an earlier FDA review<sup>45</sup> 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. Individuals prescribed ALKS 3831 who use opioids nonmedically could 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).<sup>46</sup> 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.

### **8.2.8 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

Not applicable.

### **8.2.9 Safety Analyses by Demographic Subgroups**

On review of exploratory subgroup safety analyses for AEs, there were trends of higher specific AE rates in subjects age <55 years versus  $\geq 55$  years, in females compared to males, and in subjects with BMI  $\geq 25$  kg/m<sup>2</sup> versus BMI <25 kg/m<sup>2</sup>. Of note, this subgroup analysis is based upon the Applicant's ISS randomized control pool data and analysis which includes Studies A303, A305, and also 401. This was discussed in the IND phase and was deemed acceptable as

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<sup>45</sup>FDA Office of Surveillance and Epidemiology Review, archived internally on August 4, 2017. Reference ID: 4135425.

<sup>46</sup>Morgan JR, et al. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend.* 2019; 200:34-9.

the Applicant stated no significant change with inclusion of Study 401. The expanded safety population pool may actually be beneficial for subgroup analysis given generally limited sample sizes otherwise.

### 8.2.9.1 Age Subgroups

With ALKS 3831 (and olanzapine) treatment, the age <55 years subgroup (N=447) was significantly larger than the age ≥55 years subgroup (N=73) so one should interpret the AE percentages cautiously. Overall rate of AEs was higher for the <55 years subgroup (67.8%) compared to the ≥55 years subgroup (50.7%). Subjects on ALKS 3831 age <55 years experienced a higher rate of weight increased (21.9%) compared to subjects age ≥55 years (15.1%). Other discrepancies of reported AEs between subjects in the ALKS 3831 treatment group younger than and older than 55 years were present but were also seen in the olanzapine treatment group as follows:

- Somnolence
  - ALKS 3831 group: 67 subjects (15.0%) <55 years age and 5 subjects (6.8%) >55 years age
  - Olanzapine group: 64 subjects (13.4%) <55 years age and 2 subjects (4.3%) >55 years age
- Increased appetite
  - ALKS 3831 group: 30 subjects (6.7%) <55 years age and 1 subject (1.4%) >55 years age
  - Olanzapine group: 35 subjects (7.3%) <55 years age and no subjects >55 years age
- Headache
  - ALKS 3831 group: 20 subjects (4.5%) <55 years age and one subject (1.4%) >55 years age
  - Olanzapine group: 21 subjects (4.4%) <55 years age and 1 subject (2.1%) >55 years age
- Waist circumference increased
  - ALKS 3831 group: 17 subjects (3.8%) <55 years age and no subjects >55 years age
  - Olanzapine group: 22 subjects (4.6%) <55 years age and no subjects >55 years age
- Aspartate aminotransferase increased
  - ALKS 3831 group: 8 subjects (1.8%) <55 years age and 4 subjects (5.5%) >55 years age
  - Olanzapine group: 5 subjects (1.0%) <55 years age and 3 subjects (6.4%) >55 years age

Of note, five subjects age ≥65 years (all 67 years but only one randomized to ALKS 3831 treatment) were studied in pivotal Study A305; none reported any AEs. Long-term safety pooled data did not reveal any additional signals between subgroups.

Overall, subjects age <55 years on ALKS 3831 reported total and weight increased AEs with slightly greater frequency than subjects ≥55 years. Otherwise, age-related trends in AE reporting were imbalanced in subjects taking ALKS 3831, but this was consistent with subjects taking olanzapine.

### 8.2.9.2 Sex Subgroups

With ALKS 3831 (and olanzapine) treatment, the female subgroup (N=153) was smaller than the male subgroup (N=367) so one should interpret the AE percentages cautiously. Overall rates of AEs were similar between both groups (female subjects 64.1%, male subjects 65.9%). Female subjects on ALKS 3831 experienced a higher rate of somnolence and constipation. Rates of increased appetite were also greater in female subjects compared to male subjects; however, AE rates of weight increased were similar between the two groups. Reported AEs of blood CK increased was greater in males compared to female subjects; blood insulin increased was greater in female subjects compared to male subjects. But these trends were also seen in the olanzapine treatment groups, and rates of blood glucose increased and glycosylated hemoglobin increased were similar between the two groups.

**Table 75: Gender Differences Adverse Events**

	ALKS 3831		Olanzapine	
	Female (N=153) n (%)	Male (N=367) n (%)	Female (N=147) n (%)	Male (N=379) n (%)
Any TEAE	98 (64)	242 (66)	98 (67)	271 (72)
Somnolence	26 (17)	46 (13)	20 (14)	46 (12)
Constipation	7 (5)	4 (1)	2 (1)	9 (2)
Increased appetite	15 (10)	16 (4)	7 (5)	28 (7)
Weight increased	30 (20)	79 (22)	30 (20)	103 (27)
Blood creatine phosphokinase increased	1 (1)	16 (4)	1 (1)	12 (3)
Blood insulin increased	9 (6)	5 (1)	7 (5)	6 (2)
Blood glucose increased	1 (1)	4 (1)	1 (1)	1 (<1)
Glycosylated hemoglobin increased	3 (2)	4 (1)	6 (4)	9 (2)
Blood prolactin increased	2 (1)	1 (<1)	5 (3)	2 (1)

Source: Applicant's ISS Table 142, page 273

Although rates of blood prolactin increased AEs were similar between male and female subjects on ALKS 3831 in the randomized trials, in the olanzapine group and long-term safety pooled data, rates were slightly higher in female subjects (11/262, 4.2%) than in males (3/569, <1%). This trend is supported by actual prolactin level investigations with greater proportions of female subjects experiencing elevation compared to male subjects in both active treatment groups; however, both female and male subjects on ALKS 3831 demonstrated lower rates of elevation compared to female and male subjects on olanzapine—Treatment difference was more marked in female subjects. Refer to Section 8.2.3 for detailed data from Studies A303 and A305 regarding prolactin effects.

Also of note in pivotal Studies A305 and A303, elevated triglyceride level investigation revealed

abnormal shifts less frequently for females on ALKS 3831 (47 to 49.2%) compared to olanzapine (57 to 61.4%).

Aside from blood prolactin increased, long-term safety pooled data did not reveal any additional signals between subgroups.

Overall, female subjects reported somnolence, constipation, and increased appetite with slightly greater frequency than male subjects. Investigations of CK, insulin, and prolactin were also imbalanced between female and male subjects, but these trends were consistent with subjects taking olanzapine, as well.

### 8.2.9.3 Geographic Subgroups

Geographical subpopulations are closely associated with racial subgroups in that the majority of Black subjects were from the United States. With ALKS 3831 (and olanzapine) treatment, the non-U.S. subgroup (N=106) was smaller than the U.S. subgroup (N=414) so one should interpret the AE percentages cautiously. Overall rates of AEs were greater in the U.S. subgroup compared to the non-U.S. subgroup; this trend was similar in the olanzapine treatment group. Similarly, rates of most common AEs were higher in subjects from the United States compared to subjects outside of the United States in both the ALKS 3831 and olanzapine treatment groups. Differences were most marked for the most common AEs: weight increased, somnolence, dry mouth, increased appetite, and waist circumference increased. Other discrepancies of reported AEs between subjects in the ALKS 3831 treatment group within and outside of the United States were present but were also seen in the olanzapine treatment group as follows:

- Any TEAE
  - ALKS 3831 group: 299 U.S. subjects (72.2%) and 41 non-U.S. subjects (38.7%)
  - Olanzapine group: 322 U.S. subjects (80.1%) and 47 non-U.S. subjects (37.9%)
- Weight increased
  - ALKS 3831 group: 105 U.S. subjects (25.4%) and 4 non-U.S. subjects (3.8%)
  - Olanzapine group: 131 U.S. subjects (32.6%) and 2 non-U.S. subjects (1.6%)
- Somnolence
  - ALKS 3831 group: 65 U.S. subjects (15.7%) and 7 non-U.S. subjects (6.6%)
  - Olanzapine group: 60 U.S. subjects (14.9%) and 6 non-U.S. subjects (4.8%)
- Dry mouth
  - ALKS 3831 group: 46 U.S. subjects (11.1%) and 2 non-U.S. subjects (1.9%)
  - Olanzapine group: 27 U.S. subjects (6.7%) and 3 non-U.S. subjects (2.4%)

- Increased appetite
  - ALKS 3831 group: 31 U.S. subjects (7.5%) and no non-U.S. subjects
  - Olanzapine group: 35 U.S. subjects (8.7%) and no non-U.S. subjects
- Waist circumference increased
  - ALKS 3831 group: 17 U.S. subjects (4.1%) and no non-U.S. subjects
  - Olanzapine group: 22 U.S. subjects (5.5%) and no non-U.S. subjects

Long-term safety pooled data did not reveal additional signals between subgroups.

Overall, geography-related trends in AE reporting were imbalanced in subjects taking ALKS 3831, but this was consistent with subjects taking olanzapine.

#### 8.2.9.4 Subgroup by Race

Racial subpopulations are closely associated with geographical subgroups in that the majority of Black subjects were from the United States. With ALKS 3831 (and olanzapine) treatment, the White racial subgroup (N=193) was smaller than the Black racial subgroup (N=306) so one should interpret the AE percentages cautiously; other minority subgroups were too small to interpret. Overall rate of AEs was higher for the Black subgroup compared to the White subgroup on ALKS 3831; this trend was similar in the olanzapine treatment group. Similarly, rates of weight increased, increased appetite, and waist circumference increased were higher in Black subjects compared to White subjects for those taking both ALKS 3831 and olanzapine. Other discrepancies of reported AEs between Black and White subjects in the ALKS 3831 treatment group were present but were also seen in the olanzapine treatment group as follows:

- Any TEAE
  - ALKS 3831 group: 221 Black subjects (72.2%) and 105 White subjects (54.4%)
  - Olanzapine group: 225 Black subjects (72.2%) and 128 White subjects (57.7%)
- Weight increased
  - ALKS 3831 group: 75 Black subjects (24.5%) and 27 White subjects (14.0%)
  - Olanzapine group: 92 Black subjects (32.5%) and 34 White subjects (15.3%)
- Increased appetite
  - ALKS 3831 group: 23 Black subjects (7.5%) and 5 White subjects (2.6%)
  - Olanzapine group: 24 Black subjects (8.5%) and 9 White subjects (4.1%)

- Waist circumference increased
  - ALKS 3831 group: 15 Black subjects (4.9%) and 1 White subject (1%)
  - Olanzapine group: 18 Black subjects (6.4%) and three White subjects (1.4%)

Long-term safety pooled data did not reveal any additional signals between subgroups.

Overall, race-related trends in AE reporting were imbalanced in subjects taking ALKS 3831, but this was consistent with subjects taking olanzapine.

### 8.2.9.5 Weight-based Subgroups

With ALKS 3831 (and olanzapine) treatment, the subgroup with BMI <25 kg/m<sup>2</sup> (N=220) was smaller than the overweight subgroup with BMI ≥25 kg/m<sup>2</sup> (N=300) so one should interpret the AE percentages cautiously. Overall rates of AEs were slightly greater in the BMI ≥25 kg/m<sup>2</sup> subgroup compared to the BMI <25 kg/m<sup>2</sup> subgroup; this trend was similar in the olanzapine treatment group. Rates of somnolence, dry mouth, headache, and alanine aminotransferase, aspartate aminotransferase, and blood insulin increased were slightly higher in subjects with BMI ≥25 kg/m<sup>2</sup> compared to subjects with BMI <25 kg/m<sup>2</sup> for those taking ALKS 3831. Of note, rates of weight increased AE were similar between the two BMI subgroups taking ALKS 3831.

**Table 76: Weight Group Differences in Adverse Events**

	ALKS 3831		Olanzapine	
	BMI <25 kg/m <sup>2</sup> (N=220) n (%)	BMI ≥25 kg/m <sup>2</sup> (N=300) n (%)	BMI <25 kg/m <sup>2</sup> (N=200) n (%)	BMI ≥25 kg/m <sup>2</sup> (N=326) n (%)
Any TEAE	136 (62)	204 (68)	135 (68)	234 (72)
Weight increased	44 (20)	65 (22)	45 (23)	88 (27)
Somnolence	26 (12)	46 (15)	26 (13)	40 (12)
Dry mouth	17 (8)	31 (10)	11 (6)	19 (6)
Headache	6 (3)	15 (5)	8 (4)	14 (4)
Alanine aminotransferase increased	3 (1)	13 (4)	7 (4)	6 (2)
Aspartate aminotransferase increased	3 (1)	9 (3)	4 (2)	4 (1)
Blood insulin increased	1 (1)	13 (4)	6 (3)	7 (2)

Source: Applicant's ISS, Table 148, page 293

Long-term safety pooled data did not reveal any additional signals between subgroups.

Overall, weight-related trends in AE reporting were imbalanced in subjects taking ALKS 3831 with subjects whose BMIs were  $\geq 25$  kg/m<sup>2</sup> experiencing slightly greater rates of somnolence, dry mouth, headache, and alanine aminotransferase, aspartate aminotransferase, and blood insulin increased. Of note, the latter three AEs are logical since being overweight is a risk factor for these laboratory changes.

### **8.2.10 Specific Safety Studies/Clinical Trials**

The Applicant did not conduct any specialized studies to address specific safety concerns other than Study A303 and those that are standard and reviewed by other disciplines (i.e., TQT, addiction risk, hepatic impairment, and renal impairment). Please refer to the Clinical Pharmacology and Controlled Substance Staff (CSS) reviews for detailed discussion of these studies.

Briefly, the thorough QTc Study A109, moderate hepatic impairment Study A105, and severe renal impairment Study A106 did not demonstrate new safety signals; there were no SAEs or deaths. In the moderate hepatic impairment study, rates of somnolence were greater and total AEs were reported earlier. AE severity was similarly between groups with most AEs classified as mild. The Applicant reports no clinically significant liver enzyme changes in subjects with hepatic impairment. In the severe renal impairment study, rates of the most common AEs (dizziness, nausea, abdominal pain, and lethargy) were greater in subjects with renal impairment compared to healthy controls. Investigations revealed higher rates of potentially clinically significant reduced hematocrit levels and two reports of potentially clinically significant increase in diastolic blood pressure in subjects with renal impairment, but these may have been related to underlying renal disease.

### **8.2.11 Additional Safety Explorations**

#### **8.2.11.1 Human Carcinogenicity or Tumor Development**

No human carcinogenicity data is noted in the ALKS 3831 development program, and long-term safety data for the samidorphan NME component remains limited with no significant malignancy signals thus far. Two-year animal carcinogenicity study data showed no clear evidence of a signal. Please refer to the Non-Clinical Toxicology review for detailed discussion of animal studies.

#### **8.2.11.2 Human Reproduction and Pregnancy**

See the full review in DARRTS: Date June 29, 2020 – Ref ID 4633270 by Catherine Roca, MD and Miriam Dinatale DO, Division of Pediatric and Maternal Health (DPMH). Labeling recommendations were made by DPMH.

##### *Pregnancy*

There were no clinical studies of ALKS 3831 in pregnant women so there is insufficient evidence

to make any conclusive statements about safety in pregnancy. In the entire development program, there were five reported pregnancies with direct ALKS 3831 exposure. Outcomes were only available for four of these pregnancies; one was lost to follow-up. Two of these pregnancies with known outcomes had elective abortions, and one resulted in the birth of a healthy baby. Another was diagnosed with a benign fetal foramen ovale aneurysm but was born full-term and otherwise healthy; the infant was monitored to age 3 months and ongoing for a nearly-resolved atrial septal aneurysm and small patent foramen ovale. An additional three pregnancies were to partners of male subjects: Two were without complications at time of reporting (although one of these pregnancies was twin gestation) but subsequent follow-up was unavailable, and the third was a live birth that resulted in infant death at age 38 days secondary to neglect (malnutrition and dehydration). These cases are too limited in information to draw any conclusions.

Overall published data on olanzapine use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal outcomes. Neonates exposed to antipsychotic drugs, including olanzapine, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no available data on the use of samidorphan or the combination of samidorphan and olanzapine to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

#### *Lactation*

Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk. There are no data on the effects of olanzapine on milk production. There are no data on the presence of samidorphan or the combination of olanzapine and samidorphan in human milk, the effects on the breastfed infant, or the effects on milk production.

#### *Females and Males of Reproductive Potential*

Olanzapine may increase serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.

### **8.2.11.3 Pediatrics and Assessment of Effects on Growth**

ALKS 3831 safety has not been established in the pediatric population.

### **8.2.11.4 Overdose**

Seven ALKS 3831 overdoses have been reported in clinical trials. Of these seven, two were intentional overdoses. One subject in Study A306 intentionally overdosed on 12 tablets of ALKS 3831 10 mg; she was found unresponsive and hospitalized in the intensive care unit of a psychiatric hospital for 7 days. Medical interventions included fluids, electrolytes, a diuretic, and a detoxicant over 2 days; the subject discontinued study drug and recovered without sequelae. Further context is provided in Section 8.2.7. Please also refer to Section 8.2.7 for

details of an additional overdose in Study A307; this event is difficult to assess secondary to continued data blinding and polysubstance overdose. The Applicant describes the remaining overdoses as non-serious and mild; there were no associated deaths.

### **8.2.12 Safety in the Postmarket Setting**

There is no postmarketing experience with ALKS 3831. Zyprexa postmarketing experience includes the following AEs: allergic reaction, cholestatic or mixed liver injury, diabetic coma, diabetic ketoacidosis, discontinuation reaction, Drug Reaction with Eosinophilia and Systemic Symptoms, hepatitis, jaundice, neutropenia, pancreatitis, priapism, rash, restless legs syndrome, rhabdomyolysis, stuttering, venous thromboembolic events, random cholesterol levels of  $\geq 240$  mg/dL, and random triglyceride levels of  $\geq 1000$  mg/dL.

### **8.2.13 Additional Safety Issues for Other Disciplines**

DDLO was consulted to provide expert analysis on the weight gain mitigation effects of samidorphan in ALKS 3831 compared to olanzapine; the consultant Julie Golden, MD, contributed to Sections 2 and 8.1 of this review. OSE and CSS were consulted to provide expert analysis on the opioid safety of samidorphan. Celeste Mallama PhD contributed to Section 8.2.6; please also refer to the separate OSE and CSS reviews for their detailed discussions. DPMH was consulted to provide expert analysis of pediatric and maternal health issues related to ALKS 3831; the consultants Lily Yeruk Mulugeta and Catherine Roca MD contributed to Section 8.2.11 of this review.

### **8.2.14 Integrated Assessment of Safety**

During the development program, no clinical holds for safety were issued. Three deaths occurred: One subject received ALKS 3831 treatment (cause of death COPD exacerbation); the second subject received olanzapine treatment although he did also briefly receive 2 weeks of open-label ALKS 3831 previously (cause of death alcohol poisoning); and the third subject received olanzapine treatment (cause of death heroin overdose). All three were unlikely drug-related. 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.

Commonly reported AEs occurring in  $\geq 5\%$  of subjects include: weight increased, somnolence, dry mouth, headache, anxiety, increased appetite, fatigue, infection, waist circumference increased, upper respiratory infection, extra dose administered, and blood CK increased. In Study A303, somnolence, dry mouth and fatigue occurred more frequently with ALKS 3831 treatment. Weight increased occurred less frequently in Study A303 but more frequently in Study A305. Rates for other common AEs were generally similar for both ALKS 3831 and olanzapine groups. Rates of SAEs and AEDCs were also similar between active treatment groups. Although there were single reports of pulmonary embolism and seizure, these have

been reported with use of olanzapine. Overall, there were no new safety signals demonstrated in long-term, open-label Studies A306 and A304.

Subgroup analysis in subjects taking ALKS 3831 demonstrated some imbalances:

- Subjects age <55 years had more total and weight increase AEs than those  $\geq 55$  years.
- Female subjects experienced more AEs of somnolence, constipation, and increased appetite than male subjects. Female subjects in both ALKS 3831 and olanzapine treatment groups experienced higher rates of prolactin level abnormalities compared to male subjects. Prolactin level increase was less in female and male subjects on ALKS 3831 compared to olanzapine with female subjects experiencing greater mitigating effect.
- Subjects whose BMIs were  $\geq 25$  kg/m<sup>2</sup> had greater rates of somnolence, dry mouth, headache, and alanine aminotransferase, aspartate aminotransferase, and blood insulin increased compared to subjects whose BMIs were <25 kg/m<sup>2</sup>. The latter three AEs may be directly related to weight.

Many of these discrepancies were small and should be interpreted with caution given the small sizes of some subgroups.

Investigations revealed some laboratory result and vital sign abnormalities—The majority represent likely class effects, and most differences were small. See Section 1.1 for a summary of cardiometabolic effects. Other class effects that were observed include the following:

- Liver function test mean shifts from baseline were increased but similar between the ALKS 3831 and olanzapine treatment groups; rates of potentially clinically significant values were also similar.
- Prolactin level mean shifts from baseline and rates of potentially clinically significant values were also elevated for both active treatment groups although less so in the ALKS 3831 group.
- In Study A303, rates of potentially clinically significant neutrophil and leukocyte values were also elevated but similar between groups.
- In Study A303, rate of orthostatic hypotension was slightly higher in the ALKS 3831 group compared to the olanzapine group. However, rates were similar between the two groups in Study A305, and frequency in Study A303 was actually reassuring in context of historical data from the Zyprexa PI and CATIE study.
- In Study A305, weight increase was greater with ALKS 3831 compared to olanzapine and

placebo as was proportion of subjects who experienced  $\geq 7\%$  body weight gain. However, confounding these findings are Study A305 being a short-term study not designed for weight assessment and baseline weight being higher in the olanzapine treatment group.

- QTc mean shifts from baseline were slightly elevated but similar for ALKS 3831 and olanzapine—both shifts were  $\leq 5$  msec.

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, supine heart rate occurred with slightly greater frequency. However, differential occurrence was small (ALKS 3831 4% and olanzapine  $\leq 1\%$ ), and there was no consistent trend to indicate a clinically significant signal.

Incidence of EPS as measured by scales and AEs were generally similar between ALKS 3831 and olanzapine.

In Study A303, reports of suicidal ideation were lower in the ALKS 3831 group compared to the olanzapine group. There were no reports of suicidal behavior in the pivotal studies; however, in Study A306, a subject impulsively overdosed on ALKS 3831 with suicidal intent. Additionally, in Study A303, a reported AE of homicidal ideation was reported by a subject taking ALKS 3831; although not classified as such, this may have been an AEDC.

Based upon study data from the ALKS 3831 development program, there does not appear to be a signal for ALKS 3831 abuse potential or acute withdrawal. However, draft labeling does warn against concomitant opioid use in context of samidorphan opioid antagonism. During development, there was one incident of precipitated opioid withdrawal, 18 reports of concomitant opioid use without reports of inadequate analgesia, including one report of opioid overdose, and three reports of opioid abuse during ALKS 3831 treatment (although one case was described as misrepresentation of marijuana abuse). These cases are supported by epidemiologic data suggesting a substantial subset of the indicated patient population could be at risk for 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 schizophrenia.

In summary, there are no new antipsychotic-related safety signals identified in the ALKS 3831 clinical development program. However, the potential safety concerns related to the opioid antagonism of the samidorphan component in various real-world settings of opioid use warrant careful consideration—These include the potential for precipitated withdrawal, inadequate analgesia, and opioid overdose.

### **8.3 Conclusions and Recommendations**

ALKS 3831 was studied at approved olanzapine dosages 10 to 20 mg and a fixed 10 mg samidorphan dose. Antipsychotic efficacy was demonstrated in Study ALK3831-A305—There was a statistically significant reduction in the primary efficacy endpoint PANSS score change from baseline at 4 weeks.

The Applicant submitted sufficient information to adequately assess the safety profile of ALKS 3831. In Study ALK3831-A303, there was statistically significant weight mitigation effect compared to olanzapine as demonstrated by the coprimary endpoints percent weight change from baseline and proportion of subjects who gained  $\geq 10\%$  weight from baseline. These results were not supported by favorable metabolic laboratory data trends with ALKS 3831, which may have been related to a limited study duration of 24 weeks; however, there was suggested favorable difference in SBP changes, which is likely beneficial to overall cardiovascular health. Additionally, ALKS 3831 appears to be associated with known atypical antipsychotic class effects, but no new safety signals were seen in the clinical development program. In the context of real-world concurrent opioid use, the potential negative impact of the samidorphan opioid antagonist component could pose a safety risk; the Applicant has addressed this risk in proposed labeling warnings. Review for appropriate mitigation of opioid risk is ongoing at the time of this review completion.

In totality, the direct benefit of ALKS 3831 clinical efficacy appears to outweigh the safety risks of known atypical antipsychotic effects, particularly given the potential mitigation of weight gain, and of potential concurrent opioid use in real-world settings. Therefore, the value of ALKS 3831 is justified as a new treatment option for schizophrenia and bipolar I disorder, and the review team recommends an approval action.

## 9 Advisory Committee Meeting and Other External Consultations

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The Agency convened a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 9, 2020. Three voting questions and one discussion question were presented to the Committees. The complete discussion is available in the public record via the transcript of the meeting.

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

Result: 16 Yes, 1 No, 0 Abstain

2) VOTE: Has the Applicant adequately characterized the safety profile of ALKS 3831?

Result: 13 Yes, 3 No, 1 Abstain

3) VOTE: Is labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan?

Result: 11 Yes, 6 No, 0 Abstain

4) DISCUSSION: What, if any, additional data are needed to address outstanding issues?

Individual Committee members recommended the following:

- Conducting an efficacy study on patients with bipolar I disorder—*The Division had previously agreed with the Applicant that PK bridging and clinical evidence of similar ALKS 3831 antipsychotic effectiveness to olanzapine were sufficient to support the bipolar I disorder indication.*
- Conducting a long-term weight effect study including an olanzapine comparator arm—*The Division has concluded, with support of the AC, that ALKS 3831 has demonstrated clinically meaningful weight mitigation; therefore, further study, while of academic interest, is not necessary from a regulatory perspective.*
- Conducting a study to demonstrate weight mitigation benefit with patients stable on olanzapine but experiencing weight issues and in other relevant subgroups—*ALKS 3831 is broadly indicated for patients with schizophrenia and bipolar I disorder without a qualifier for prior medication status or weight; therefore, further study, while of academic interest, is not necessary from a regulatory perspective. Further the fact that patients on stable olanzapine therapy were not specifically studied so the weight effect*

*of switching from olanzapine to ALKS 3831 is unknown is included in labeling Section 14 (Clinical Studies).*

- Careful consideration of labeling details to clearly convey limitation of use (i.e., patients on olanzapine who experienced weight gain were not studied) and weight mitigation rather than weight loss—*ALKS 3831 is clearly indicated for patients with schizophrenia and bipolar I disorder without any weight qualifier. Further weight gain data is included within labeling, and the fact that patients on stable olanzapine therapy were not specifically studied so the weight effect of switching from olanzapine to ALKS 3831 is unknown is included in labeling Section 14 (Clinical Studies).*
- Conducting a PET occupancy study to better characterize samidorphan and metabolite opioid receptor pharmacodynamics—*The Division has deemed the PK/PD data sufficient to justify safe and effective treatment for schizophrenia and bipolar I disorder; therefore, further study, while of academic interest, is not necessary from a regulatory perspective.*
- Ascertainment of long-term concurrent opioid use safety data—*The Division has deemed labeling sufficient to mitigate opioid safety risks; therefore, further long-term study, while of academic interest, is not necessary from a regulatory perspective.*
- Careful consideration of labeling details to clearly convey opioid safety risks—*Inclusion of opioid safety risk within labeling has been carefully reviewed by the Division in collaboration with OSE and CSS.*

## 10 Pediatrics

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The Applicant and FDA agreed to the following Pediatric Study Plan: 1) a multiple-dose safety, tolerability, and PK study in children 10 to 12 years of age with bipolar I disorder 2) a (b) (4) double-blind, olanzapine-controlled, (b) (4) change in BMI study in children 13 to 17 years of age with schizophrenia or 10 to 17 years of age with bipolar I disorder and 3) a 12-month, open-label, safety extension study. A Written Request was also issued for these studies and is under review at the time of this review completion.

## 11 Labeling Recommendations

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### 11.1 Prescription Drug Labeling

#### Prescribing information

At the time of review completion, the Prescribing Information (PI) is being sent for negotiation with the Applicant. The following clinical recommendations for changes to the proposed label have been made to the Applicant:

- Indications and Usage: Indications were clarified to schizophrenia in adults and bipolar disorder in adults 1) with manic and mixed episodes as either monotherapy or adjunctive therapy to valproate or lithium and 2) for maintenance monotherapy.
- Dosage and Administration: The section [REDACTED] (b) (4) was removed [REDACTED] (b) (4) [REDACTED]
- Warnings and Precautions:
  - [REDACTED] (b) (4)
  - Metabolic Changes: This section was generally truncated to provide a general statement about glycemic, lipid, and body weight changes; additional warning regarding hyperglycemia aligning with language from the olanzapine label was also added. Reference is made to Sections 6 Adverse Reactions where the metabolic data was transposed.
  - [REDACTED] (b) (4) This section was updated to Anticholinergic (Antimuscarinic) Effects to more precisely describe the issue, to detail risk factors, and to be consistent with the LD PI.
- Adverse Reactions:
  - [REDACTED] (b) (4) removed for consistency with this section's objective of presenting ALKS 3831 common AEs [REDACTED] (b) (4)

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- Similarly, [REDACTED] (b) (4) was removed and replaced by text listing of all AEs occurring in  $\geq 2\%$  of subjects taking ALKS 3831. Additional AEs of blood pressure increased, neutrophil count decreased, weight decreased, extra dose administered, back pain, vomiting, dyslipidemia, and blood prolactin increased were added because of incidence  $\geq 2\%$ . The additional AEs leading to ALKS 3831 discontinuation schizophrenia and liver function test abnormal were added because of occurrence in greater than one subject.
- Study ALK3831-A305 weight data and Studies ALK3831-A305 and ALK3831-A303 metabolic data were relocated to this section as deemed more appropriate as safety data. Additional glycemc data from Study ALK3831-A303 was added to provide a more complete picture of potential changes.
- Use in Specific Populations: Language in Pregnancy, Lactation, and Females and Males of Reproductive Potential sections were updated in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).
- Clinical Studies:
  - Study ALK3831-A303 was delineated a Special Safety Study marking its distinction from the antipsychotic efficacy study supporting the indications claims. Weight data from ALK3831-A303 was presented in this section [REDACTED] (b) (4)
  - A clarifying note that olanzapine-stable patients were not studied was included.

## **12 Risk Evaluation and Mitigation Strategies (REMS)**

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In conjunction with OSE and CSS, the Division considered appropriate risk mitigation to address the risks of concurrent opioid use. A primary concern includes targeting non-prescribing clinicians of ALKS 3831 for education regarding the samidorphan opioid antagonist component of this novel combined product—In other words, prescribers and patients would not be the target population for risk mitigation education. Impact of an educational program targeting non-prescribing clinicians would also likely not be feasible. Therefore, REMS programming is not an appropriate means to address the stated concern. Furthermore, previously approved products consisting of an opioid antagonist have not included a REMS plan nor has potential risk with concomitant medication use justified utilization of REMS programming to-date. The Agency has determined that labeling is sufficient to mitigate risks with ALKS 3831 and that a REMS plan is not necessary.

### 13 Postmarketing Requirements and Commitment

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- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Perform a lactation study (milk only), in lactating women who have received therapeutic doses of ALKS 3831, using a validated assay to assess concentrations of olanzapine and concentrations of samidorphan in breast milk [REDACTED] (b) (4)

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#### **14 Division Director (OB) Comments**

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None.

#### **15 Division Director (Clinical) Comments**

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See separate Summary Memo.

#### **16 Office Director (or designated signatory authority) Comments**

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See separate Summary Memo.

## 17 Appendices

### 17.1 References

See footnotes.

### 17.2

### 17.3 Financial Disclosure

#### Covered Clinical Studies: ALK3831-A305 and ALK3831-A303

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>44</u> investigators for ALK3831-A305, <u>68</u> investigators for ALK3831-A303		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>10</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>10</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in: <u>1</u></p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		

Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)
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## 17.4 Additional Study Analysis Results

### 17.4.1 Study 303: Body Composition Substudy

An exploratory substudy was conducted to measure body composition using bioelectrical impedance analysis (BIA)<sup>47</sup> at baseline and at the end of treatment in subjects at a subset of sites. Subjects could be enrolled if they were in A303 at a site equipped with a body composition analyzer, consented to have body composition analysis, and did not have an electronic implant or device (e.g, pacemaker, infusion pump), or any active or powered prostheses.

The substudy was planned to be conducted in up to 200 subjects participating in A303. However, only 19 subjects in the ALKS 3831 group and 17 subjects in the olanzapine group had both baseline and postbaseline assessments of body composition and are therefore included. Given this large amount of missing data, the substudy results are difficult to interpret. A summary of the results are provided for completeness.

The following exploratory endpoints were assessed<sup>48</sup>:

- Absolute change from baseline in lean mass
- Absolute change from baseline in fat mass
- Change from baseline in percent body fat
- Total skeletal muscle mass
- Torso skeletal muscle mass
- Visceral adipose tissue

No differences between groups were observed for any of the body composition parameters.

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<sup>47</sup> Using the Seca Medical Body Composition Analyzer (mBCA 514)

<sup>48</sup> These endpoints were analyzed by the ANCOVA method adjusting for race (black or African American, not black or African American), and baseline age (<30, ≥30 years) as factors, and the corresponding baseline value as covariate for the subset of subjects with baseline and post baseline body composition assessments. Since there were only baseline and end-of-treatment assessments, the ANCOVA model was applied without imputation for missing data.

**Table 77. Body Composition Substudy (Study A303)**

	ALKS 3831 N=19	OLZ N=17
Lean mass, kg		
Baseline, n	19	16
Mean baseline (SD)	55.92 (8.730)	54.28 (8.149)
Week 24, n	15	16
Week 24 mean change from baseline (SD)	0.42 (3.054)	1.51 (2.164)
LS Mean difference ALKS 3831 – OLZ (95% CI)	-1.06 (-2.94, 0.81)	
Fat mass, kg		
Baseline, n	19	17
Mean baseline (SD)	18.54 (9.119)	17.78 (8.698)
Week 24, n	15	17
Week 24 mean change from baseline (SD)	1.56 (3.750)	3.64 (4.916)
LS Mean difference ALKS 3831 – OLZ (95% CI)	-2.11 (-5.46, 1.25)	
Percent body fat		
Baseline, n	19	16
Mean baseline (SD)	24.09 (9.589)	24.45 (10.206)
Week 24, n	15	16
Week 24 mean change from baseline (SD)	1.01 (3.167)	2.22 (4.511)
LS Mean difference ALKS 3831 – OLZ (95% CI)	-1.29 (-4.28, 1.69)	
Total skeletal muscle mass, kg		
Baseline, n	17	17
Mean baseline (SD)	27.75 (4.899)	28.30 (8.453)
Median baseline (min, max)	27.80 (19.4, 39.2)	27.49 (16.6, 55.4)
Week 24, n	13	17
Week 24 LS mean change from baseline (SE)	2.18 (1.324)	2.97 (1.264)
LS Mean difference ALKS 3831 – OLZ (95% CI)	-0.78 (-3.05, 1.48)	
Torso skeletal muscle mass, kg		
Baseline, n	16	17
Mean baseline (SD)	12.50 (2.531)	13.41 (4.477)
Median baseline (min, max)	12.83 (7.9, 17.8)	12.40 (6.3, 25.8)
Week 24, n	12	17
Week 24 LS mean change from baseline (SE)	0.80 (0.296)	0.56 (0.284)
LS Mean difference ALKS 3831 – OLZ (95% CI)	0.24 (-0.28, 0.76)	
Visceral adipose tissue, L		
Baseline, n	16	17
Mean baseline (SD)	1.70 (1.362)	8.53 (14.468)
Median baseline (min, max)	1.20 (0.0, 4.9)	1.90 (0.7, 40.8)
Week 24, n	13	16
Week 24 LS mean change from baseline (SE)	0.06 (6.240)	-1.66 (5.987)
LS Mean difference ALKS 3831 – OLZ (95% CI)	1.72 (-9.36, 12.80)	

Source: A303 CSR, Tables 14.2.23.1, 14.2.23.2, 14.2.23.3 and A303 CSR addendum, Table 6

### 17.4.2 Study A108

The Applicant conducted a 3-week metabolic study (A108) to further characterize ALKS 3831 on insulin sensitivity and other metabolic parameters in comparison to olanzapine and placebo in 60 healthy volunteers. Some of the assessments included height, weight, body composition using DEXA, fasting glucose, insulin, and lipids, leptin, oral glucose tolerance test (OGTT), mixed meal tolerance test (MMTT), euglycemic-hyperinsulinemic clamp, energy intake and expenditure measurements, and substrate oxidation.

Some of the key results were reported as follows:

- Subjects treated with ALKS 3831 gained 3.2 kg, olanzapine 2.3 kg, and placebo 0.6 kg body weight and 2.0 kg, 1.8 kg, and 0.6 kg body fat, respectively, over the 3-week treatment period.
- Mean changes in fasting glucose were -5.0 mg/dL for ALKS 3831, -7.5 mg/dL for olanzapine, and -8.4 mg/dL for placebo, and changes in fasting insulin were +1.16  $\mu$ U/mL, +1.22  $\mu$ U/mL, and -0.85  $\mu$ U/mL, respectively. Changes in homeostasis model assessment-insulin resistance (HOMA-IR), a model used to estimate insulin resistance (lower numbers are better), were +0.22, +0.11, and -0.35, respectively. All confidence intervals overlapped.
- In the OGTT, the olanzapine treatment group showed increases in insulin AUC of approximately 41% and increases in C-peptide at Day 19 compared to baseline. Hyperinsulinemia was not observed for the ALKS 3831 or placebo groups. In the MMTT, elevations in postprandial insulin were observed in the olanzapine group at Day 18 relative to baseline, whereas all treatment groups showed increases in C-peptide.
- In the OGTT, the ALKS 3831 and olanzapine groups showed increases in glucose AUC at Day 19 compared to baseline, but these increases were not different from placebo. In the MMTT, ALKS 3831, olanzapine, and placebo treatment groups all had increases in glucose AUC, with no differences between groups.
- In the hyperinsulinemic-euglycemic clamp, decreases in the insulin sensitivity index (lower numbers are worse) were observed for the ALKS 3831, olanzapine, and placebo treatment groups at both Day 10 and Day 21 compared to baseline, with olanzapine and ALKS 3831 showing greater decreases than placebo at Day 10.
- Mean changes for ALKS 3831, olanzapine, and placebo treatment groups for fasting cholesterol were +18.9, +13.9, -4.8 mg/dL, respectively; fasting LDL-C +23.7, +20.4, +2.3 mg/dL respectively; fasting HDL-C -5.4, -9.4, and -7.1 mg/dL, respectively; fasting TG +2.0, +11.3, +1.0 mg/dL respectively; and fasting leptin +2.31, +2.09, +0.33 ng/mL, respectively. Confidence intervals overlapped for all ALKS 3831 versus olanzapine comparisons.

- Olanzapine and ALKS 3831 showed elevations in postprandial TG AUC and de-novo lipogenesis.
- Although the ALKS 3831 treatment group showed a decrease in caloric intake on Day 22 compared to baseline versus the olanzapine and placebo treatment groups (both of which showed non-significant increases in total caloric intake), interpretation of the results is complicated by differential baseline measured caloric intake (highest in the ALKS 3831 group and lowest in the placebo group).
- Olanzapine was associated with an increase in respiratory quotient that was not observed with ALKS 3831 or placebo. Olanzapine was also associated with a numerically greater increase in resting energy expenditure relative to ALKS 3831 and placebo (67.9 kcal per day for olanzapine compared to 19.4 and 20.0 kcal/day respectively). Carbohydrate oxidation increased by 30.1 g/day for the olanzapine group compared to changes of -3.1 and +2.0 g/day for the placebo and ALKS 3831 groups, respectively, and fat oxidation decreased by 11.3 g/day for the olanzapine group compared to increases of 6.0 and 1.2 g/day for the placebo and ALKS 3831 groups, respectively.
- There was a baseline race imbalance observed with randomization such that the ALKS 3831 group and placebo group showed a roughly equal distribution between white and black subjects whereas the majority of the olanzapine group was white (83%).

The results of this exploratory study suggest that metabolic disturbances occur early in treatment with both olanzapine and ALKS 3831 (e.g., in weight, fasting lipid, fasting glucose metabolism, and insulin sensitivity as measured by the hyperinsulinemic-euglycemic clamp). There was some suggestion that olanzapine, but not ALKS 3831, demonstrated increases in postprandial insulin after a mixed meal challenge and an increased respiratory quotient. Whether these findings reflect the long-term metabolic effects of ALKS 3831 in the schizophrenic or bipolar populations is unclear.

Finally, it should be noted that in a 3-week proof-of-concept study in healthy male volunteers (ALK33-301), which evaluated samidorphan 5 mg, olanzapine 10 mg, olanzapine 10 mg/samidorphane 5 mg, and placebo, subjects taking olanzapine/samidorphane gained less weight from baseline (+2.2 kg) than those taking olanzapine alone, (+3.1 kg;  $p=0.020$ ); however, the change in glucose was greatest in the samidorphan-alone arm (+0.36 mmol/L), followed by placebo (+0.09 mmol/L), olanzapine-alone (-0.01 mmol/L), and olanzapine/samidorphane (-0.09 mmol/L). These results suggest that a 3-week timepoint, particularly in healthy individuals, might not exhibit adequate trial sensitivity to identify the impact of samidorphan on olanzapine for weight and other metabolic parameters. In Study 33-301, weight gain was less with the combination versus olanzapine alone, but this was not observed in Study A108. Furthermore, blood glucose changes over these short time periods should be interpreted with caution given

that mean blood glucose decreased in the olanzapine-containing groups and increased in the placebo and samidorphan-alone groups.

Table 78 summarizes changes in weight with olanzapine/samidorphan, olanzapine only, and placebo in studies of 3 to 4 weeks duration.

**Table 78: Weight Change in 3- to 4-Week Studies**

	OLZ+SAM	OLZ	Placebo
<b>Study ALK33-301, 21 days</b> SAM dose = 5 mg			
N	34	35	17
Baseline weight (SD), kg	67.54 (7.66)	68.11 (7.21)	70.91 (9.77)
Weight change (SD), kg	+2.23 (1.352)	+3.11 (1.879)	+0.82 (1.421)
<b>Study A108, 22 days</b> SAM dose = 10 mg			
N	24	24	12
Baseline weight (SD), kg	70.95 (7.940)	70.56 (7.757)	69.58 (6.871)
Weight change (SE), kg	+3.22 (0.423)	+2.31 (0.405)	+0.57 (0.626)
<b>Study A305, 4 weeks</b> SAM dose = 10 mg			
N	134	133	134
Baseline weight (SD), kg	77.86 (15.426)	82.24 (19.309)	76.64 (15.915)
Weight change (SD), kg	+3.02 (3.564)	+2.38 (3.653)	+0.24 (2.757)

Source: ALK33-301 CSR, Table 14.2.6.4; A108 CSR, Table 9; A305 CSR, Table 34

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Clinical, Stats, DDLO reviews linked.

BERNARD A FISCHER  
11/13/2020 04:57:08 PM  
CDTL/Supervisory Physician

# Office of Clinical Pharmacology Review

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<b>NDA or BLA Number</b>	213378
<b>Link to EDR</b>	<a href="#">Application 213378 - Sequence 0001 - 0001 (1) 11/15/2019 ORIG-1 /Multiple Categories/Subcategories</a>
<b>Submission Date</b>	11/15/19
<b>Submission Type</b>	Standard Review
<b>Brand Name</b>	Lybalvi
<b>Generic Name</b>	Olanzapine and Samidorphan
<b>Dosage Form and Strength</b>	Oral Immediate Release (IR) tablets Olanzapine:Samidorphan = 5/10, 10/10, 15/10 and 20/10 mg
<b>Route of Administration</b>	Oral
<b>Proposed Indication</b>	Treatment of schizophrenia and bipolar 1 disorder
<b>Applicant</b>	Alkermes
<b>Associated IND</b>	IND-114375, (b)(4) and NDA- (b)(4)
<b>OCP Review Team</b>	Praveen Balimane, Vishnu Sharma, Atul Bhattaram, Yuching Yang, Manuela Grimstein, Luning (Ada) Zhuang
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## **1. EXECUTIVE SUMMARY**

This is a New Drug Application (NDA) for an NME-505(b)(2) combination product - ALKS 3831. It is an oral, fixed-dose combination of olanzapine (OLZ) and samidorphan (SAM), for the treatment of schizophrenia and bipolar I disorder. OLZ is a previously approved atypical antipsychotic and SAM is a new molecular entity (NME) that has not been approved in the past in the U.S. The purpose of SAM in ALKS 3831 combination product is to mitigate OLZ-induced weight gain issue in patients. SAM does not impact the antipsychotic efficacy of OLZ. The 505(b)(2) pathway for ALKS 3831 relies in part on the US Food and Drug Administration's (FDA) prior findings of safety and effectiveness for the listed drug (LD), Zyprexa (NDA 020592; OLZ). The NDA is submitted by Alkermes and the proposed trade name is LYBALVI.

ALKS 3831 is available as an immediate release (IR) tablet in the following strengths of OLZ/SAM: 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg. ALKS 3831 is proposed to be administered once daily with or without food and following the dosage and administration guidelines of the LD, Zyprexa.

The pivotal registration package for this NDA includes two Phase 3, randomized, double-blind, active- and/or placebo-controlled studies:

- Study A305: A Phase 3 Study to Determine the Antipsychotic Efficacy and Safety of ALKS 3831 in Adults with Acute Exacerbation of Schizophrenia
- Study A303: A Phase 3 Study to Evaluate Weight Gain of ALKS 3831 Compared to OLZ in Adults with Schizophrenia

Additionally, there are four long term open label studies (A304, A306, A307, A308) that assessed the safety of the combination product. The detailed analysis of benefits: risk assessment of the combination product is covered in the medical review (Clinical review in Darrrts: Cathy Southammakosane *et.al.*; NDA 213378).

ALKS 3831 was used for all the key clinical pharmacology studies such as – single ascending and multiple ascending dose study, organ impairment studies, food effect study, TQT study, and drug-interaction studies. Additionally, several clinical pharmacology studies including the mass-balance study as well as the abuse-potential studies were performed with SAM alone.

A dedicated study (A101) provided a PK-bridging to support the 505(b)(2) pathway of OLZ. The study demonstrated that bioequivalence of OLZ was achieved for ALKS 3831 and the LD, Zyprexa. A dedicated PK study (33-301) demonstrated that OLZ does not impact the PK of SAM and SAM also does not impact the PK of OLZ. A dedicated food-effect study demonstrated that the PK of either SAM or OLZ is not impacted by presence of high-fat and high-protein food.

***Note:*** In different section of the review/appendix the NDA product is inter-changeably referred to as- ALKS 3831, OLZ/SAM, and LYBALVI.

## 1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA package. The decision to support the approval of the product depends on the benefits: risk assessment to be performed by the medical team.

The key review issues with specific recommendations and comments are summarized below:

Key Review Issue	Recommendations and Comments
<p><b>Pivotal or supportive evidence of effectiveness</b></p>	<ul style="list-style-type: none"> <li>• Study A305 was a phase 3 study to determine the antipsychotic efficacy and safety of ALKS 3831 in adults with acute exacerbation of schizophrenia. It demonstrated that ALKS 3831 had statistically significant efficacy compared to placebo. ALKS 3831 efficacy was similar to OLZ alone.</li> <li>• Study A303 was a phase 3 study to evaluate weight gain of ALKS 3831 compared to OLZ in adults with schizophrenia. The study results met both the pre-defined co-primary end points (% change in body weight and proportion of patients with &gt;10% weight gain). However, the lack of any changes in the metabolic parameters (i.e., fasting lipid and glucose parameters) coupled with a small effect-size has raised questions regarding the clinical relevance of the extent of weight change.</li> </ul>
<p><b>Is the proposed dosing regimen for general patient population acceptable?</b></p>	<ul style="list-style-type: none"> <li>• Both the pivotal efficacy studies (A305 and A303) were conducted using the same flexible dose strategy with a starting dose of 10 mg/10 mg (OLZ/SAM) followed by gradual up-titration of dose based on tolerability up to a max dose of 20 mg/10 mg. The proposed dosage and administration criteria are identical to the one used in the pivotal efficacy trials. Therefore, the proposed dosing regimen is acceptable.</li> </ul>
<p><b>Are the proposed dose-adjustments for organ impaired patients acceptable?</b></p>	<ul style="list-style-type: none"> <li>• Study A106 was a dedicated renal impairment (RI) study which assessed the effect of “severe” renal impairment on the PK of ALKS 3831. Both OLZ and SAM had increase in exposure in renal impaired vs. normal subjects. OLZ had ~50% increase whereas SAM had 2x fold increase. Based on available safety data, 2x fold increase in exposure of SAM is not expected to be associated with additional safety concern. Therefore, no dose adjustments are recommended for mild, moderate or severe RI patients.</li> </ul>

	<p>It is not recommended for patients with End-Stage Renal Disorder (ESRD). Details are provided in Section 3.3</p> <ul style="list-style-type: none"> <li>• Study A105 was a dedicated hepatic impairment study which assessed the effect of “moderate” hepatic impairment on the PK of ALKS 3831. Both OLZ and SAM had increase in exposure in hepatic impaired vs. normal subjects. OLZ had ~70% increase whereas SAM had ~50% increase. Though “severe” HI subjects were not included in the study, PBPK analysis was performed to estimate the magnitude of increase in SAM exposure anticipated in “severe” HI patients. PBPK analysis predicted a 2.6x fold increase in exposure of SAM in “severe” HI. This was comparable with a 2.1x fold increase in exposure of SAM observed in “severe” HI subjects in a dedicated study (b) (4)</li> </ul> <p>Based on available safety data, 2-2.5x fold increase in exposure of SAM is not expected to be associated with additional safety concern. Additionally, there is no dose adjustments recommended for ZYPREXA in hepatic impaired patients. Therefore, we agree that no dose adjustment is required for ALKS 3831 in HI. Details are provided in Section 3.3.</p>
<p><b>Is the data from the Physiologically-based Pharmacokinetic (PBPK) analysis adequate to support the labelling for drug interactions with strong CYP3A4 inhibitors?</b></p>	<ul style="list-style-type: none"> <li>• Study 33-B107 was a dedicated single dose mass-balance study performed in healthy volunteers with SAM alone. It demonstrated that SAM metabolized via multiple CYP pathways primarily via CYP3A4 and 3A5 and minor via CYP2C8 and 2C19. Study A103 was a dedicated study to assess the effect of CYP3A induction (via rifampin) on the PK of SAM. However, a dedicated study was not conducted to assess the effect of strong CYP3A4 inhibition on the PK of SAM. No dose adjustment is needed for OLZ in the approved OLZ label with concomitant use with strong CYP3A inhibitors. PBPK analysis indicated that a strong CYP3A4 inhibitor (such as itraconazole), may increase exposure of SAM by 60%. Additionally, a dedicated drug interaction study had been conducted (b) (4)</li> </ul> <p>Itraconazole was shown to result in 45% increase in exposure of SAM. Therefore, we agree no dose adjustment is required. Details are provided in Section 3.3</p>

## 1.2 Post-Marketing Requirements and Commitments

None at this time.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

### 2.1 Pharmacology

LYBALVI is a fixed-dose combination of OLZ and SAM. The exact mechanism of action of OLZ is unknown. However, it has been proposed that its efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT<sub>2</sub>) antagonism. SAM binds with high affinity to human  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors and acts primarily as an antagonist at  $\mu$  receptors, with low intrinsic activity at  $\kappa$  and  $\delta$  receptors. No significant binding is noted on dopamine and 5HT<sub>2</sub> receptors, which are known to play a role in antipsychotic efficacy. These findings suggest that SAM alone has no antipsychotic properties. Rather, the opioid antagonism conferred by SAM is intended to mitigate weight gain associated with OLZ treatment.

### 2.2 Dosing and Therapeutic Individualization

#### 2.2.1 General dosing

ALKS 3831 is administered orally, once daily, and without regard to food.

For Schizophrenia: ALKS 3831 (OLZ/SAM mg/mg) can be started at 5/10 or 10/10. The recommended dose is 10/10, 15/10, or 20/10.

For Bipolar I Disorder (Manic or Mixed Episodes): ALKS 3831 can be started at 10/10 or 15/10. The recommended dose is 10/10, 15/10, or 20/10. ALKS 3831 can be used as an adjunct to lithium or valproate without the need for dose adjustment.

#### 2.2.2 Therapeutic individualization

- Renal Impairment (RI): Based on the results from a dedicated RI study (details in Section 3.3), the following dose-adjustment strategies are recommended:
  - Mild, moderate and severe RI = no dose adjustment
  - End-Stage Renal Disorder (ESRD) = not recommended
- Hepatic Impairment (HI): Based on the results from multiple clinical dataset (including a dedicated HI study) and PBPK modeling approach (details in Section 3.3), the following dose-adjustment strategies are recommended:
  - Mild, moderate and severe HI = no dose adjustment

- Concomitant administration with CYP3A4 inducers: Based on a dedicated drug interaction study (details in Section 3.3), ALKS 3831 is not recommended to be concomitantly administered with CYP3A4 inducers.
- Concomitant administration with CYP3A4 inhibitors: Based on PBPK modeling approach and past clinical data (details in Section 3.3), no dose-adjustment is recommended for ALKS 3831 on concomitant administration with CYP3A4 inhibitors.
- Concomitant administration with CYP1A2 inhibitors: Based on the Zyprexa label, reduced dosage of ALKS 3831 is recommended on concomitant administration with CYP1A2 inhibitors.

### **2.3 Outstanding Issues**

None at this time.

### **2.4 Summary of Labeling Recommendation**

Based on the review, the Office of Clinical Pharmacology made the following concrete recommendations:

- Concrete dose adjustments for renal impaired patients.
- Concrete dose adjustments for hepatic impaired patients.
- Concrete dose adjustments for concomitant administration with CYP3A4 inducers and inhibitors.

The detailed dose adjustment strategies for all clinical scenarios are provided in Section 3.3.

### **3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW**

#### **3.1 Overview of the Product and Regulatory Background**

ALKS 3831 is an oral, fixed-dose combination of OLZ and SAM intended for the treatment of schizophrenia and bipolar I disorder. OLZ is an atypical antipsychotic. SAM functions as an opioid receptor antagonist and is included to mitigate OLZ-induced weight gain. SAM does not impact the antipsychotic efficacy of OLZ. ALKS 3831 is a bilayer tablet containing OLZ and SAM L-malate drug substances.

ALKS 3831 is a film coated, immediate-release bilayer tablet, with one layer containing OLZ and the other layer containing SAM. The following dosage strengths are available:

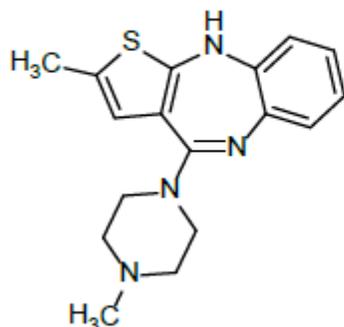
- 5 mg OLZ/10 mg SAM (ALKS 3831 5/10)
- 10 mg OLZ/10 mg SAM (ALKS 3831 10/10)
- 15 mg OLZ/10 mg SAM (ALKS 3831 15/10)
- 20 mg OLZ/10 mg SAM (ALKS 3831 20/10)

SAM 10 mg free base is equivalent to 13.6 mg samidorphan L-malate, the drug substance used in the ALKS 3831 product.

#### **3.2 General Pharmacology and Pharmacokinetic Characteristics**

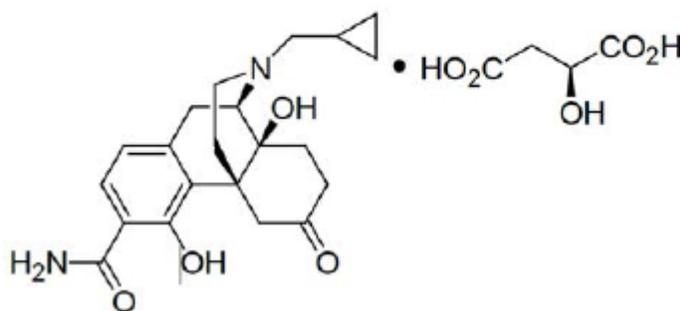
<b>Pharmacology</b>
<p><u>Mechanism of Action:</u></p> <ul style="list-style-type: none"><li>• The exact mechanism of action of OLZ is unknown. However, it has been proposed that its efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism.</li><li>• SAM binds with high affinity to human <math>\mu</math>-, <math>\kappa</math>-, and <math>\delta</math>-opioid receptors and acts primarily as an antagonist at <math>\mu</math> receptors, with low intrinsic activity at <math>\kappa</math> and <math>\delta</math> receptors. No significant binding is noted on dopamine and 5HT2 receptors, which are known to play a role in antipsychotic efficacy. These findings suggest that SAM alone has no antipsychotic properties. Rather, the opioid antagonism conferred by SAM is intended to mitigate weight gain associated with OLZ treatment.</li></ul>
<p><u>Active Moieties:</u></p> <ul style="list-style-type: none"><li>• OLZ is the only active moiety for anti-psych efficacy. Though there are 2 major circulating metabolites (with exposure ~30% of the parent), they are both inactive.</li></ul>

**Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine)**



- SAM is the only active moiety for the mitigation of weight gain. Though there are 2 major circulating metabolites (with exposure ~35% of the parent), they are both inactive.

**Samidorphan L-malate (morphinan-3-carboxamide, 17-(cyclopropylmethyl)-4,14-dihydroxy-6-oxo-,(2S)-2-hydroxybutanedioate)**



QT prolongation:

- ALKS 3831 at supratherapeutic doses (up to 30/30) and plasma concentrations did not have a clinically relevant effect on ECG parameters, including QT interval. The upper bound of the 90% confidence interval (CI) of the predicted placebo-corrected change from baseline in corrected QT interval using Fridericia's formula ( $\Delta\Delta QTcF$ ) did not exceed 10 msec at any of the geometric mean peak concentrations of OLZ or SAM across the dose range evaluated (10/10, 20/20, and 30/30).

**Key General Information**

Bioanalysis:

- Both OLZ and SAM and their metabolite concentrations in plasma and urine were measured using validated LC-MS/MS methods. The summary of method validation reports is provided in the appendix.

Drug exposure (for OLZ and SAM) at steady state

- Mean steady state exposures at the highest recommended therapeutic dose of 20 mg /10 mg of ALKS 3831 (i.e., 20 mg OLZ and 10 mg SAM)
  - OLZ at 20 mg

<ul style="list-style-type: none"> <li>▪ C<sub>max,ss</sub> = ~65 ng/mL</li> <li>▪ AUC<sub>0-24h, ss</sub> = ~1090 ng*h/mL</li> <li>○ SAM at 10 mg <ul style="list-style-type: none"> <li>▪ C<sub>max,ss</sub> = ~46 ng/mL</li> <li>▪ AUC<sub>0-24h, ss</sub> = ~360 ng*h/mL</li> </ul> </li> </ul>
<p><u>Dose Proportionality:</u></p> <ul style="list-style-type: none"> <li>• PopPK analysis indicated linear PK of OLZ and SAM over a range of 5 to 30 mg for each drug.</li> </ul>
<p><u>Accumulation Index at steady state</u></p> <ul style="list-style-type: none"> <li>• OLZ concentrations reached steady state in about 1 week with an accumulation index of ~2- fold.</li> <li>• SAM concentrations reached steady state in about 5 days, with a low accumulation index (&lt; 1.4- fold).</li> </ul>
<p><u>PK in healthy vs. PK in patients:</u></p> <ul style="list-style-type: none"> <li>• No difference in OLZ and SAM PK between healthy subjects and subjects with schizophrenia was identified by PopPK analysis.</li> </ul>
<p><b><u>Clinical ADME</u></b></p>
<p><b>Absorption</b></p>
<p><b>OLZ</b></p> <ul style="list-style-type: none"> <li>• OLZ was well absorbed with median time to maximum plasma concentration (T<sub>max</sub>) observed at 4.5 to 7 hours following an oral dose of ALKS 3831.</li> <li>• The bioavailability of OLZ after a single oral dose of ALKS 3831 10/10 was equivalent to that of Zyprexa 10 mg.</li> </ul> <p><b>SAM</b></p> <ul style="list-style-type: none"> <li>• SAM was rapidly absorbed with median T<sub>max</sub> observed at 1 to 2 hours following an oral dose of ALKS 3831.</li> <li>• Although an absolute bioavailability study has not been conducted with SAM, mass balance study suggest that the absorption of SAM is ~70% (because ~70% of oral dose is eliminated via the urine, as a combination of parent and metabolites).</li> </ul>
<p><b>Distribution</b></p>
<p><b>OLZ</b></p> <ul style="list-style-type: none"> <li>• OLZ was 93% bound to plasma protein over a concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α1-acid glycoprotein.</li> <li>• It has a high mean apparent volume of distribution (V<sub>z</sub>/F) ranging from 769 L to 1550 L.</li> </ul> <p><b>SAM</b></p> <ul style="list-style-type: none"> <li>• Plasma protein binding of SAM was low, ranging from 23% to 33%</li> <li>• It has a mean apparent volume of distribution (V<sub>z</sub>/F) of ~ 340 L</li> </ul>
<p><b>Metabolism</b></p>
<p><b>OLZ</b></p>

- OLZ was extensively metabolized. The primary metabolic pathways for OLZ were direct glucuronidation and CYP-mediated oxidation, mainly by CYP1A2.
- After multiple dosing, the major circulating metabolites were the 10-N-glucuronide (44% of OLZ) and 4'-N-desmethyl-OLZ (31% of OLZ). Both metabolites lack pharmacological activity at the concentrations observed.

#### **SAM**

- The primary metabolic pathways for SAM N-dealkylation and N-oxidation, mainly by CYP3A4.
- After multiple dosing, the major circulating metabolites were RDC-9986, a des-cyclopropyl-methyl metabolite, and RDC-1066, an N-oxide metabolite (both ~35% of SAM) Both metabolites lack pharmacological activity at the concentrations observed

#### **Elimination**

#### **OLZ**

- After a single oral dose of [14C] OLZ, approximately 57% and 30% of the dose were recovered in the urine and feces, respectively.
- The CL/F of OLZ was approximately 15 to 22 L/hr
- T1/2 is 35-52 hr

#### **SAM**

- Following a single 2-mg oral dose of [14C]-SAM, on average, approximately 67% and 16% of radioactivity were recovered in the urine and feces, respectively.
- Approximately 18% of the dose was excreted in urine as unchanged SAM, while RDC-9986 accounted for most of the remaining radioactivity in urine, comprising 25% of the administered dose.
- The CL/F of SAM ranged from approximately 35 to 45 L/hr
- T1/2 is 7-11 hr

### 3.3 Clinical Pharmacology Review Questions

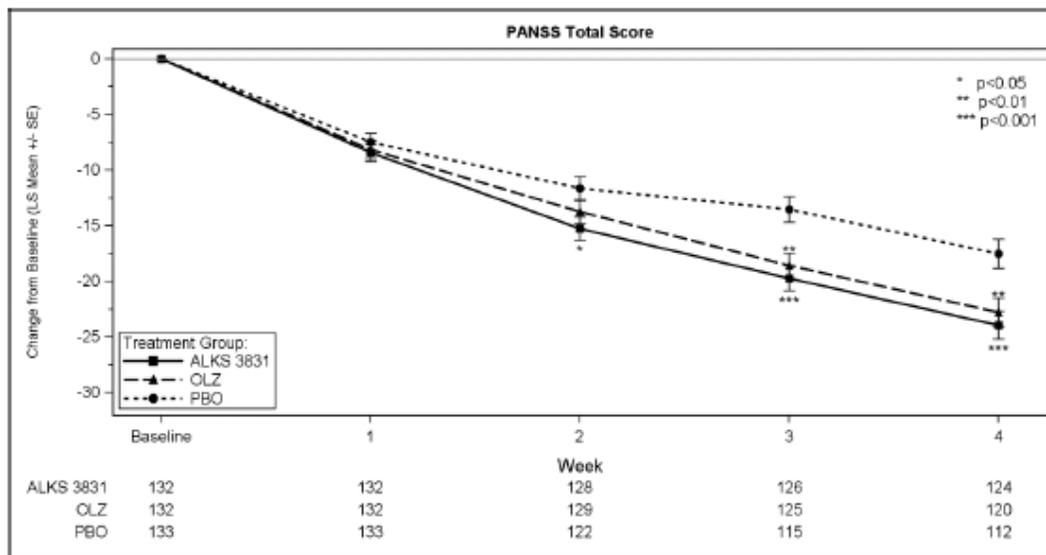
#### 3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Evidence of effectiveness is supported primarily by 2 pivotal studies- A305 and A303.

#### Evidence of antipsychotic efficacy

- Study A305 was a Phase 3, multinational, multicenter, randomized, double-blinded study in acutely ill, hospitalized subjects with schizophrenia. This study was conducted at 38 sites in the US, Bulgaria, Ukraine, and Serbia. Subjects were randomized 1:1:1 to ALKS 3831, OLZ, or placebo. The primary efficacy endpoint was change from baseline in PANSS total score at Week 4. The key secondary endpoint was change from baseline in CGI-S score at Week 4. The aim of the study was to assess the antipsychotic efficacy and safety of ALKS 3831 in adults with acute exacerbation of schizophrenia. ALKS 3831 met the prespecified primary endpoint, demonstrating statistically significant reductions from baseline in PANSS total score compared to placebo at Week 4 (least squares [LS] mean [standard error {SE}] difference -6.4 [1.83];  $P<0.001$ ). The active control, OLZ, also demonstrated a statistical separation from placebo at Week 4 (-5.3 [1.84];  $P=0.004$ ), which was numerically similar to that observed with ALKS 3831. The key secondary endpoint was also met the pre-specified criteria.

Figure 1: Study A305: LS Mean Change From Baseline in PANSS by Visit



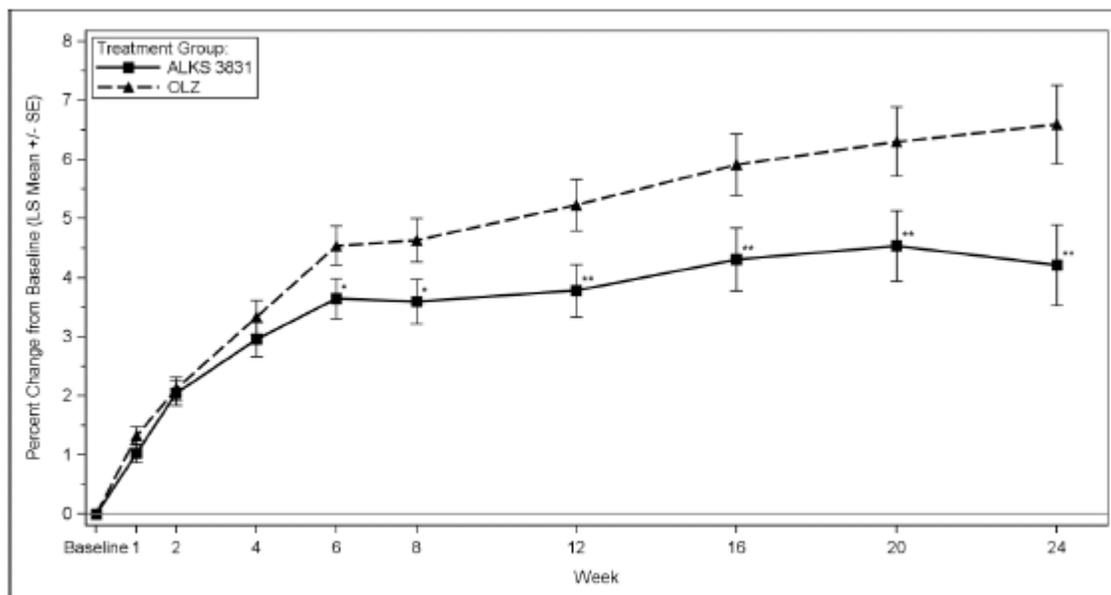
Abbreviations: FAS=full analysis set; LS mean=least squares mean; MMRM=mixed model for repeated measures; OLZ=olanzapine; PANSS=Positive and Negative Syndrome Scale; PBO=placebo; SE=standard error  
 Notes: The numbers under the graph indicate the number of subjects at each time point.  
 LS mean change from baseline at Week 2 was statistically significant at  $\alpha=0.05$  for ALKS 3831 but not for OLZ.  
 Both ALKS 3831 and OLZ treatments showed significant differences from PBO at Week 3 and Week 4.

Source: 2.7.3 Summary of Clinical Efficacy, Page 32

## Evidence of efficacy regarding weight-gain advantage

- Study A303 was a Phase 3, multicenter, randomized, double-blinded study in stable outpatients with schizophrenia, conducted at 64 sites within the US. The co-primary endpoints were the percent change from baseline in body weight at Week 24 and the proportion of subjects with  $\geq 10\%$  weight gain at Week 24 in the full analysis set (FAS) population. The key secondary endpoint was the proportion of subjects with  $\geq 7\%$  weight gain at Week 24. The study was designed to evaluate weight gain of ALKS 3831 compared to OLZ in adults with schizophrenia. The ALKS 3831 group met the prespecified co-primary endpoints, with significantly less weight gain relative to OLZ, based on the percent change from baseline in body weight at Week 24 (LS mean [SE] difference  $-2.38\%$  [ $0.765\%$ ]; adjusted  $P=0.003$ ) and a smaller proportion of subjects with clinically meaningful weight gain ( $\geq 10\%$ ) from baseline at Week 24. The ALKS 3831 group had a smaller percent change in body weight compared to the OLZ Group starting at Week 6 and remained stable thereafter, whereas continued weight gain was observed in the OLZ group over the 24-week treatment period. However, the lack of any changes in the metabolic parameters (i.e., fasting lipid and glucose parameters) coupled with a small effect-size has raised questions regarding the clinical relevance of the weight change.

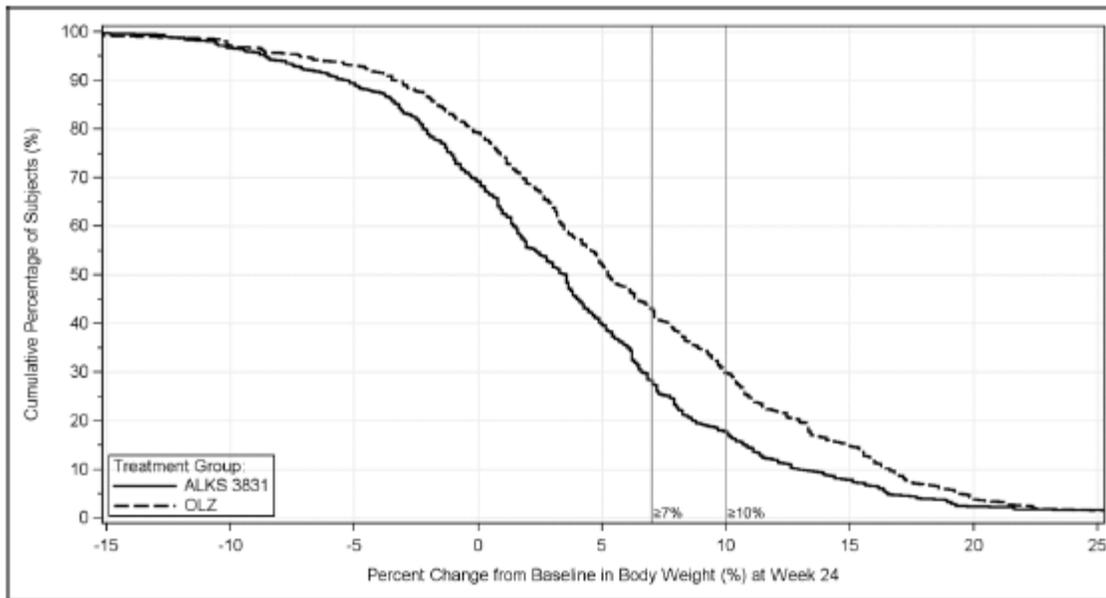
**Figure 2: LS Mean of Percent Change From Baseline in Body Weight by Visit**



Abbreviations: ANCOVA=analysis of covariance; FAS=full analysis set; LS=least squares; MI=multiple imputation; OLZ=olanzapine; SE=standard error; vs=versus  
\*\* $P < 0.01$  vs OLZ; \* $P < 0.05$  vs OLZ.

Source: 2.7.3 Summary of Clinical Efficacy, Page 44

**Figure 3: Cumulative Frequency Distribution of Percent Change From Baseline in Body Weight at Week 24**



Abbreviations: FAS=full analysis set; MI=multiple imputation; OLZ=olanzapine

Source: 2.7.3 Summary of Clinical Efficacy, Page 46

Additional evidence of antipsychotic efficacy was provided via study A303 and a phase 2 study-302. Similarly, additional evidence of the efficacy in limiting weight gain of ALKS 3831 was provided by Study 302.

The detailed analysis of benefits: risk assessment of the combination product is covered in the medical review (Clinical review in Dartrts: Cathy Southammakosane *et.al.*; NDA 213378).

### 3.3.2 *Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes, the proposed dosing regimen is appropriate for the general population for the indications being sought (schizophrenia and bipolar I disorder). The dosing regimen is consistent with the LD, Zyprexa. The approved doses of OLZ are 5 to 20 mg per day. The effective dose range of OLZ for the treatment of schizophrenia is the same as that for the treatment of bipolar I disorder.

A fixed dose of 10 mg SAM in combination with OLZ has demonstrated antipsychotic efficacy and optimal mitigation of OLZ-induced weight gain in patients with schizophrenia. The evidence that ALKS 3831 mitigates OLZ-induced weight gain relies primarily on the pivotal Study A303. It is also supported by evidence of mitigation of weight gain in a Phase 2 study (Study 302) in subjects with schizophrenia.

### 3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Though samidorphan PK in patients is not impacted by age, sex, race, or smoking status, the PK of olanzapine is impacted by age, sex and smoking status. However, no dose adjustments are recommended due to the intrinsic factors for ALKS 3831. Please refer to **Error! Reference source not found.** for all details.

#### Patients with renal impairment (RI):

Study A106 was a dedicated open-label study to assess the effect of severe RI on the PK, safety, and tolerability of a single oral dose of ALKS 3831 5/10. A total of 20 subjects, 10 subjects with severe RI (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m<sup>2</sup>) and 10 healthy control subjects (creatinine clearance  $\geq$ 90 mL/min), were enrolled in the study. Healthy control subjects were matched to subjects with severe RI based on median age, BMI, and sex. All subjects were administered a single oral dose of ALKS 3831 5/10 on Day 1. For PK assessments, serial blood samples were collected pre-dose and up to 168 hours post-dose. Mean plasma concentrations of OLZ and SAM were higher in subjects with severe RI compared to healthy control subjects after a single oral dose of ALKS 3831.

**Table 1: Increase in systemic exposures (i.e., fold increase) of OLZ and SAM in “severe” renal impaired subjects vs. healthy control subjects**

Moiety	Fold increase in AUC	Fold increase in Cmax
OLZ	1.3x	1.5x
SAM	1.4x	2.3x

Source: Summary of Clinical Pharmacology, Page# 36

The results from this study were found to be consistent with the historical data: results in renal impaired subjects (b) (4) as well as results in renal impaired subjects with Zyprexa alone. Additionally, evaluation of SAM at doses greater than 10 mg did not reveal any new safety findings. In Study ALK33-003, which assessed SAM alone at 10 mg and 20 mg doses in healthy volunteers, the pattern of AEs was generally consistent across doses and there was no obvious dose effect. Similar findings were observed in Studies 302 and A109, evaluating SAM, at doses of up to 30 mg, in combination with OLZ in patients with schizophrenia. The consistency in the types of AEs across multiple doses of SAM suggests that 2x fold higher exposure of SAM are not expected to be associated with new safety concerns. Thus, a 2x fold increase in exposure of SAM observed in severe RI subjects does not require any dose adjustments.

Based on these results, no dose adjustment is recommended for mild, moderate or severe RI patients. However, since the study did not include any subjects with End-Stage Renal Disorder (ESRD), ALKS 3831 is not recommended for patients with ESRD.

### Patients with hepatic impairment (HI):

Study A105 was a Phase 1, multicenter, open-label, parallel cohort study to assess the effect of moderate HI on the PK, safety, and tolerability of a single dose of ALKS 3831 5/10. A total of 21 subjects, 10 subjects with moderate HI (Child-Pugh [CP] score of 7 to 9; class B) and 11 healthy control subjects were enrolled in the study. Healthy control subjects were matched to subjects with moderate HI based on median age, body mass index (BMI), and sex. All subjects were administered a single oral dose of ALKS 3831 5/10 as a bilayer tablet on Day 1. Serial blood samples for PK assessments were collected pre-dose and up to 168 hours post-dose. Mean plasma concentrations of OLZ and SAM were higher in subjects with moderate HI compared to healthy control subjects after a single oral dose of ALKS 3831 5/10.

**Table 2: Increase in systemic exposures (i.e., fold increase) of OLZ and SAM in “moderate” hepatic impaired subjects vs. healthy control subjects**

Moiety	Fold increase in AUC	Fold increase in Cmax
OLZ	2.2x	1.7x
SAM	1.6x	1.5x

Source: Summary of Clinical Pharmacology, Page# 33

The results from this study were found to be consistent with historical data: results in hepatic impaired subjects [REDACTED] (b) (4)

The current HI study was conducted in “moderate” hepatic impaired subjects and thus no data was generated in “severe” HI subjects. PBPK modeling and simulations were conducted to predict the exposure of SAM in subjects with mild, moderate and severe HI. The SAM HI PBPK model was supported with data from the clinical study [REDACTED] (b) (4). The modeling and simulations predicted steady state Cmax and AUC ratios for samidorphan in subjects with severe HI relative to subjects with normal hepatic function were 2.1 and 2.6, respectively. Refer to the PBPK review in Section 4.3 for details. The prediction is consistent with the results from the clinical HI study [REDACTED] (b) (4) in “severe” HI [REDACTED] (b) (4) which indicate SAM Cmax and AUC increase of 1.5x fold and 2.1x fold, respectively in patients with severe HI. . Additionally, there is no dose adjustments recommended for ZYPREXA in hepatic impaired patients.

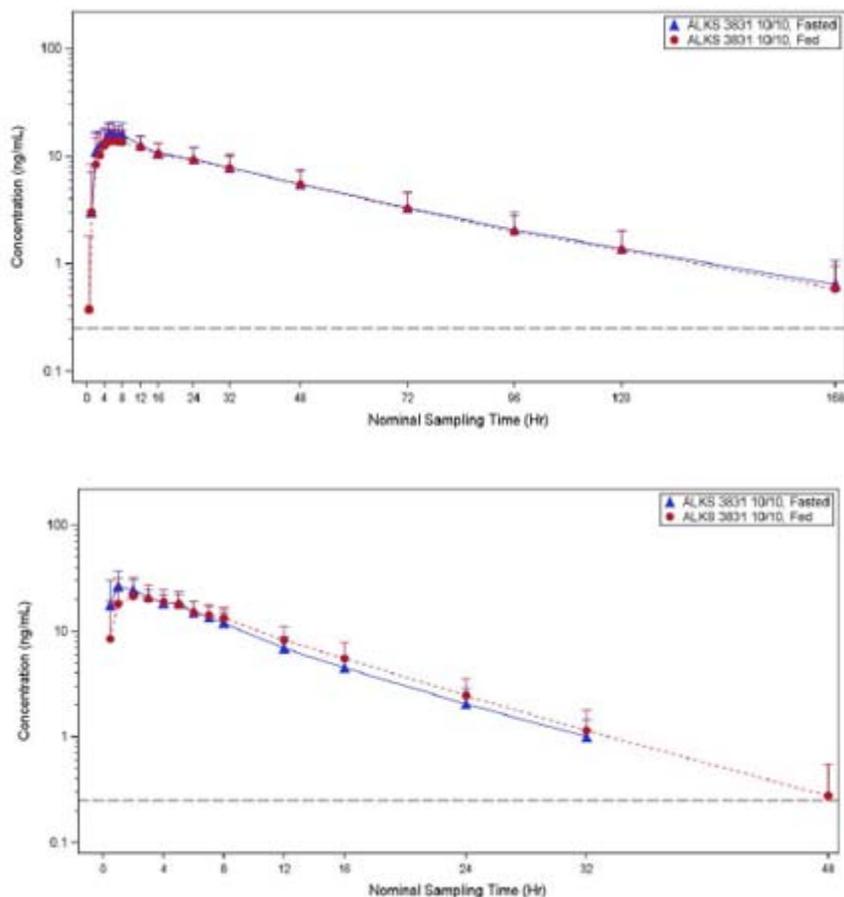
Based on these results, and safety data that suggests that 2x fold higher exposure of SAM are not expected to be associated with new safety concerns , no dose adjustment is recommended for mild, moderate or severe HI patients.

### **3.3.4 Are there clinically relevant food-drug or drug-drug interactions (DDI’s) with ALKS 3831 and what is the appropriate dose management strategy?**

Food effect study: There were no clinically relevant food-drug interactions with either OLZ or SAM. A dedicated study (A107) demonstrated that a high-fat meal did not affect the rate or extent of OLZ or SAM absorption when the two drugs were administered in combination as ALKS 3831. Therefore, ALKS 3831 can be taken with or without food. The findings with ALKS 3831 were also consistent with findings of no effect of food on OLZ and SAM PK when each drug was administered alone.

Based on no effect of food, ALKS 3831 can be taken with or without food.

*Figure 4: Plasma concentration of OLZ and SAM (mean + standard deviation) in fed and fasted state (Study A107)*



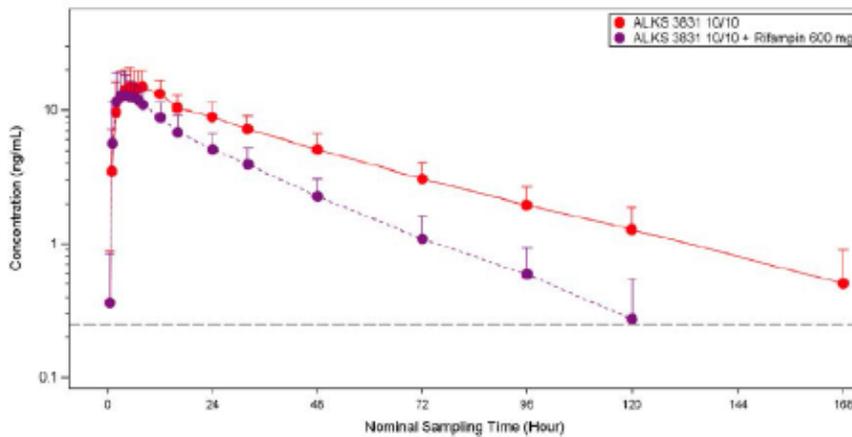
Source: Sponsor report- Final study report for A107, Page # 38, 47.

Drug interaction with CYP3A4 inducers: Study A103 was a Phase 1, single-center, open-label, two-period study evaluating the effect of rifampin, a potent CYP3A4 inducer, on the single-dose PK of ALKS 3831 in 24 healthy adult subjects. Following a single oral dose of ALKS 3831, the mean plasma concentration-time profiles of OLZ and SAM were lower in the presence of rifampin than in the absence of rifampin. Coadministration with rifampin, a strong CYP3A4

inducer, decreased total systemic exposure (based on  $AUC_{\infty}$ ) of SAM and OLZ by 73% and 48%, respectively.

Based on a 73% reduction in AUC of SAM in presence of CYP3A4 inducers and the fact that ALKS 3831 is available only at a single strength of SAM (i.e., 10 mg), ALKS 3831 is not recommended for concomitant use in presence of CYP3A4 inducers.

**Figure 5: Plasma Concentrations (Mean + Standard Deviation) of Olanzapine with or without Rifampin.**

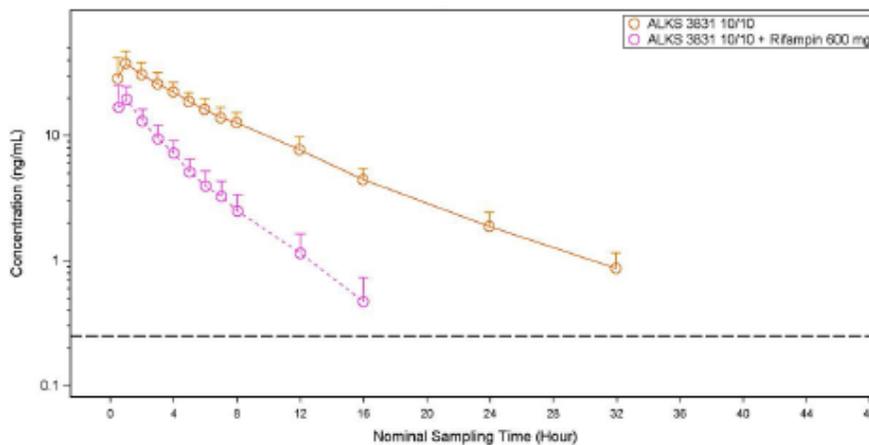


Abbreviation: LLOQ=lower limit of quantification.

Note: Predose times have been set to zero. Individual values below the LLOQ have been set to zero in the calculation of the summary statistics. The calculated mean values <LLOQ are not presented. The dashed line indicates the value of LLOQ.

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Page 40

**Figure 6: Plasma Concentrations (Mean + Standard Deviation) of Samidorphan with or without Rifampin.**



Abbreviation: LLOQ=lower limit of quantification.

Note: Predose times have been set to zero. Individual values below the LLOQ have been set to zero in the calculation of the summary statistics. The calculated mean values <LLOQ are not presented. The dashed line indicates the value of LLOQ.

Drug interaction with CYP3A4 inhibitors: Though a dedicated drug interaction study was not conducted, the PBPK analysis was considered adequate to predict the interaction potential of SAM with strong CYP3A4 inhibitors. Refer to the PBPK review in Section 4.3 for details. PBPK analysis predicted that concomitant administration of a single oral dose of samidorphan with multiple doses of itraconazole, a strong CYP3A4 inhibitor, may increase exposure of SAM by approximately 1.3 and 1.6- fold for C<sub>max</sub> and AUC, respectively. Additionally, a dedicated drug interaction study had been conducted (b) (4)

Itraconazole was shown to have only marginal increase in exposure of SAM (~16% increase in C<sub>max</sub> and ~45% increase in AUC)

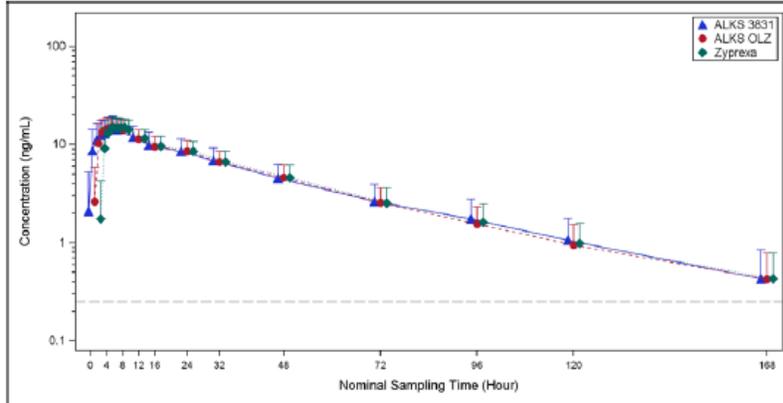
Based on the concurrence of the PBPK analysis and the past clinical data, no dose-adjustment is recommended for ALKS 3831 on concomitant administration with CYP3A4 inhibitors.

Drug interaction with CYP1A2 inhibitors and Inducers: SAM gets metabolized via the CYP3A4 pathway and has no interaction with the CYP1A2 enzymes. The dosage adjustments recommended for ALKS 3831 on concomitant administration with CYP1A2 inhibitors and inducers are based on the effect on OLZ concentrations and thus are same as Zyprexa label.

### ***3.3.5 Was there an adequate PK bridging established from the combination product (ALKS 3831) to the Listed Drug, Zyprexa?***

Yes, a dedicated PK study (A101) was conducted to determine the relative bioavailability of olanzapine after single dose oral administration of ALKS 3831, ALKS OLZ (Alkermes olanzapine), and the listed drug, Zyprexa®. The mean plasma concentration-time profile of olanzapine following a single oral administration of ALKS 3831 10/10, ALKS OLZ 10/0 or Zyprexa 10 mg demonstrated that PK profile was practically super-imposable for the combination product, ALKS 3831 vs. the listed drug, Zyprexa.

***Figure 7: Plasma Concentrations of Olanzapine (Mean + Standard Deviation) for the three treatments: ALKS 3831, ALKS OLZ and Zyprexa***



Note: Values below the lower limit of quantification (<LLOQ) have been set to zero in the calculation of the summary statistics. Values below LLOQ values are not presented. LLOQ is presented as dashed line.

Source: Clinical Study Report A101, Fig 3, Page# 42.

Statistical comparisons of relative bioavailability of olanzapine between ALKS3831 vs. Zyprexa are summarized in table below. The geometric mean ratios were close to 1 and the 90% confidence intervals (CIs) of the geometric mean ratios were contained completely within the bioequivalence limit of 80%-125%, indicating exposure of olanzapine met the bioequivalence criteria.

**Table 3: Results of Evaluation of Bioequivalence of Olanzapine Pharmacokinetic Parameters: Comparing ALKS 3831 to the LD, Zyprexa**

Parameter Statistics	Treatment Group		
	ALKS 3831 (10 mg Olz/10 mg Sam) (N=46)	ALKS OLZ (10 mg Olz/Pbo) (N=45)	Zyprexa (10 mg Olz) (N=48)
<b>AUC<sub>∞</sub> (hr*ng/mL)</b>			
n	44	44	46
Geometric Mean (SE)	627.907 (0.047)	606.961 (0.047)	610.370 (0.047)
Geometric Mean Ratio	1.029	0.994	-
90% CI	(0.995, 1.063)	(0.962, 1.028)	-
<b>AUC<sub>last</sub> (hr*ng/mL)</b>			
n	45	44	47
Geometric Mean (SE)	594.368 (0.048)	578.933 (0.048)	578.890 (0.048)
Geometric Mean Ratio	1.027	1.000	-
90% CI	(0.993, 1.062)	(0.967, 1.034)	-
<b>C<sub>max</sub> (ng/mL)</b>			
n	45	45	47
Geometric Mean (SE)	16.291 (0.037)	16.310 (0.037)	16.391 (0.037)
Geometric Mean Ratio	0.994	0.995	-
90% CI	(0.954, 1.036)	(0.955, 1.037)	-

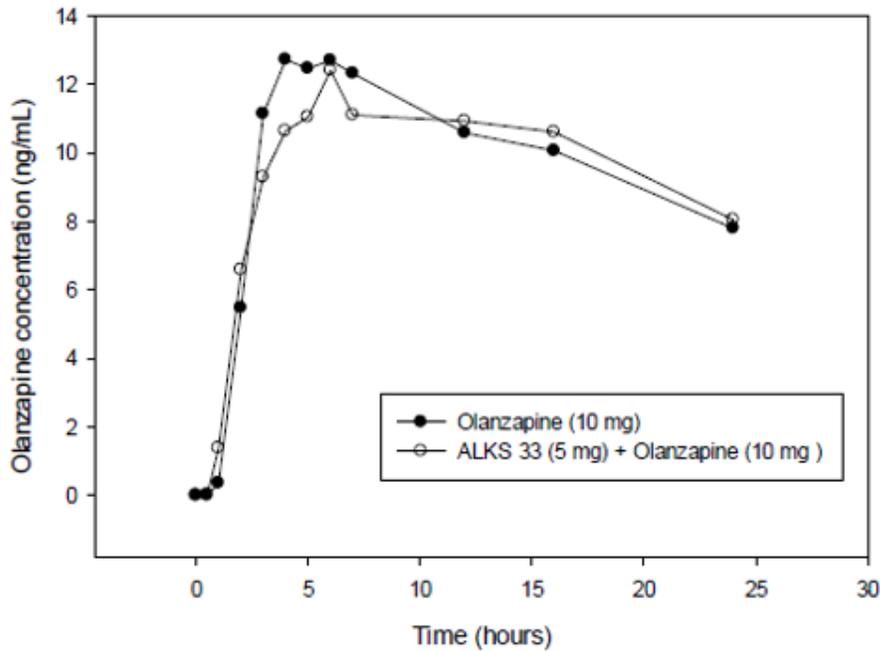
CI=Confidence Interval; N=number of subjects who received a specific treatment; n=number of subjects whose parameter values are included in the summary statistics; Olz=Olanzapine; Pbo=Placebo; Sam=Samidorphan; SE=standard error (the SE displayed is in natural log scale).

Source: Clinical Study Report ALK3831-A101, Page 60

**3.3.6 Were there any drug interactions observed between the two components of the combination product: SAM and OLZ?**

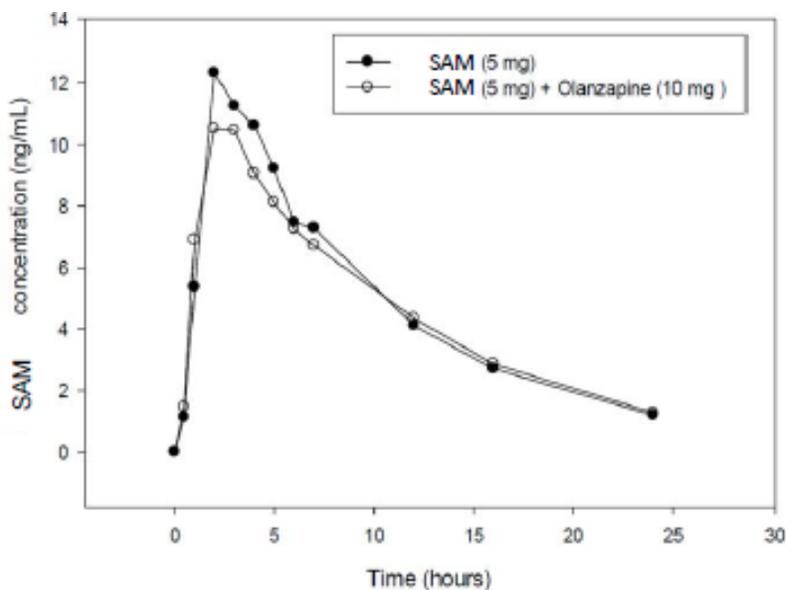
A dedicated PK study (33-301) demonstrated that SAM and OLZ has no drug interactions and they did not impact each other's PK. The systemic exposure (C<sub>max</sub> and AUC<sub>0-24</sub>) to OLZ were similar when OLZ was administered alone and in combination with SAM (OLZ + SAM). Similarly, systemic exposure to SAM was also similar when SAM was administered alone and in combination with OLZ (OLZ+ SAM). The results indicated that there was no PK DDI between OLZ and SAM, which is consistent with the distinct metabolic pathways of OLZ and SAM.

**Figure 8: Mean Olanzapine Concentrations Following Administrations of Olanzapine Alone and in Combination with Samidorphan (Study 33-301)**



Source: Clinical Study Report 33-301, fig 6, Page 60.

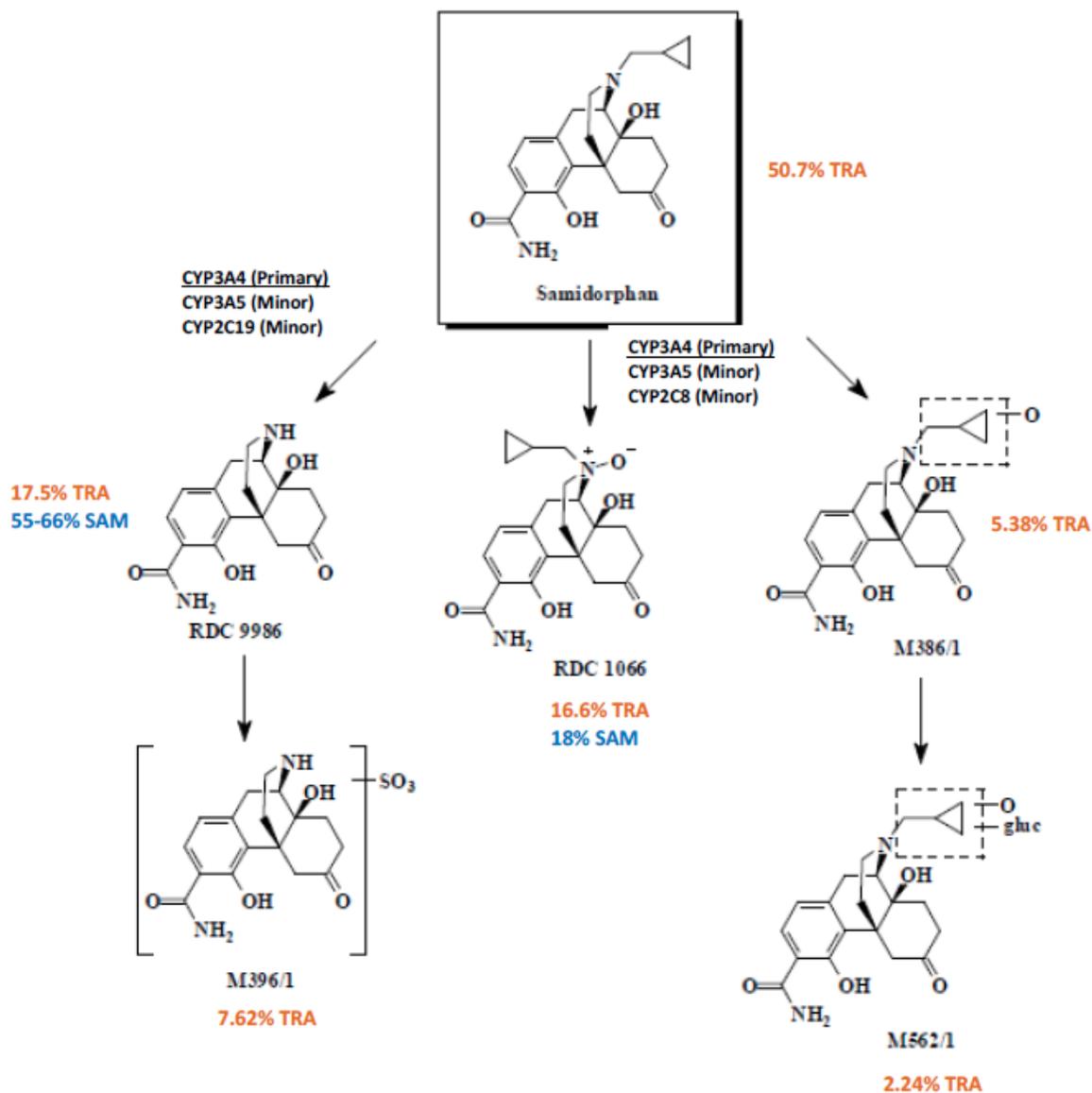
**Figure 9: Mean Samidorphan Concentrations Following Administrations of Samidorphan Alone and in Combination with Olanzapine (Study 33-301)**



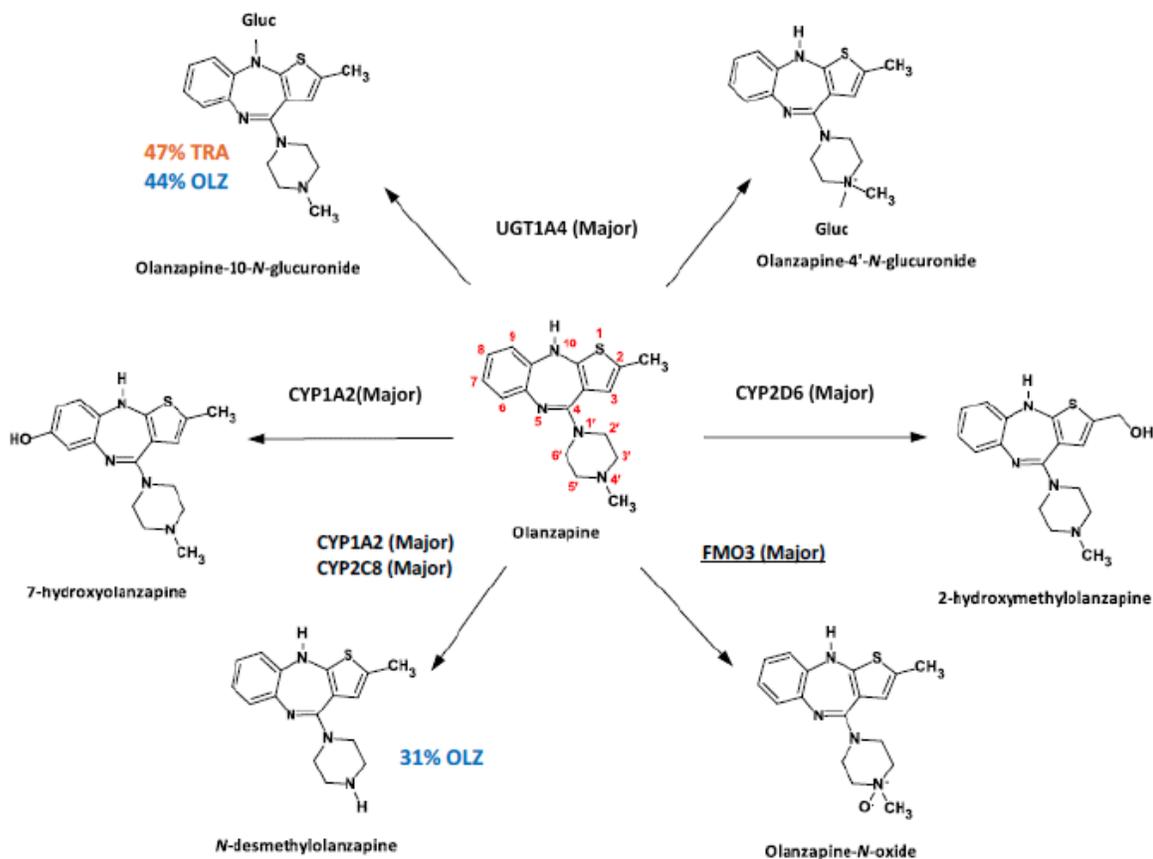
Source: Clinical Study Report 33-301, fig 4, Page 56.

In addition to the direct PK study, a detailed assessment of the metabolic pathways of metabolism of the two components also demonstrated that OLZ and SAM have very unique and distinct enzymatic pathways involved in their metabolism which explains the lack of any drug interactions. SAM is mainly metabolized via the CYP3A4 where as OLZ underwent direct glucuronidation and CYP-mediated oxidation, mainly by CYP1A2. Additionally, both SAM and OLZ and their circulating metabolites were non inhibitors of major CYP enzymes.

***Figure 10: Metabolic pathway of SAM and OLZ in human***



Abbreviations: CYP=cytochrome P450; gluc=glucuronide; UGT= uridine 5'-diphospho-glucuronosyltransferase.  
 Notes: % TRA=percent total radioactivity in human plasma following a 2 mg single oral dose of [<sup>14</sup>C]-SAM (based on AUC<sub>0-24h</sub> in pooled plasma sample); % SAM=percent of steady state parent drug (SAM) exposure in human plasma following once daily oral doses of OLZ/SAM (10/10 or 20/10) (based on steady state AUC<sub>0-24h</sub>) Source:



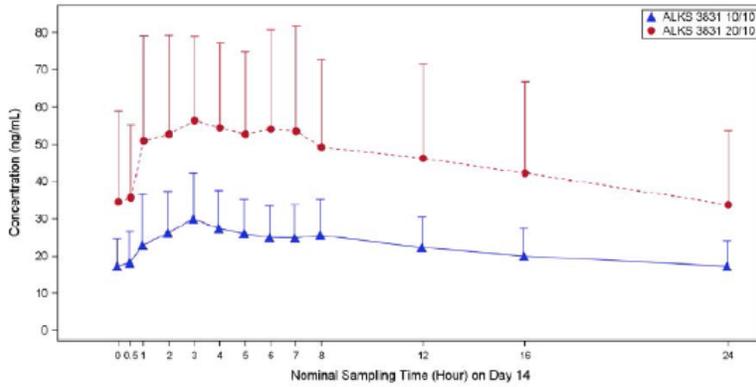
Abbreviations: CYP=cytochrome P450; gluc=glucuronide; UGT= uridine 5'-diphospho-glucuronosyltransferase.  
 Note: %TRA in human plasma following a single oral dose of [<sup>14</sup>C]-OLZ (Kassahun et al, 1997); % OLZ = percent of parent drug (olanzapine) concentration in human plasma at steady state after multiple dosing (Zyprexa USPI).

Source: Sponsor's- 1.11.3 Clinical Information Amendment, Fig 3 & 4, Page 7-10.

### 3.3.7 Is the single dose and steady state PK of combination product (ALKS 3831) characterized adequately?

Yes, the single dose and steady state PK have been fully characterized. This is supported by the fact that the PK of OLZ and SAM over the clinical dose range of ALKS 3831 5/10 to 20/10 and up to a supratherepatic dose of 30/30 have been evaluated after oral administration of ALKS 3831. Single and multiple dose PK has been assessed in both healthy adult subjects as well as patients with schizophrenia in the therapeutic dose range. Representative plots of steady state PK of OLZ and SAM are listed below.

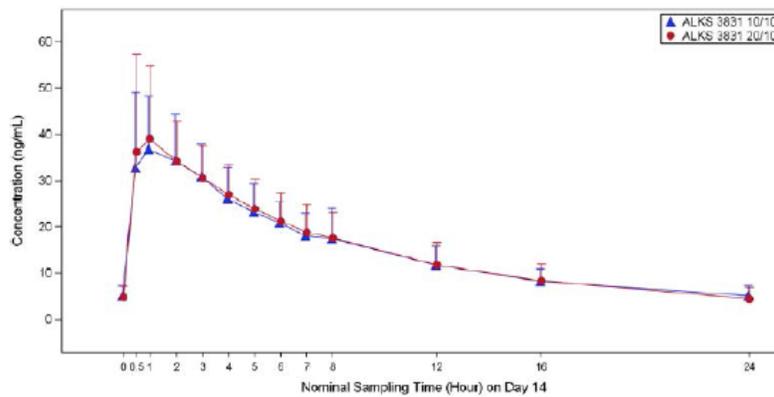
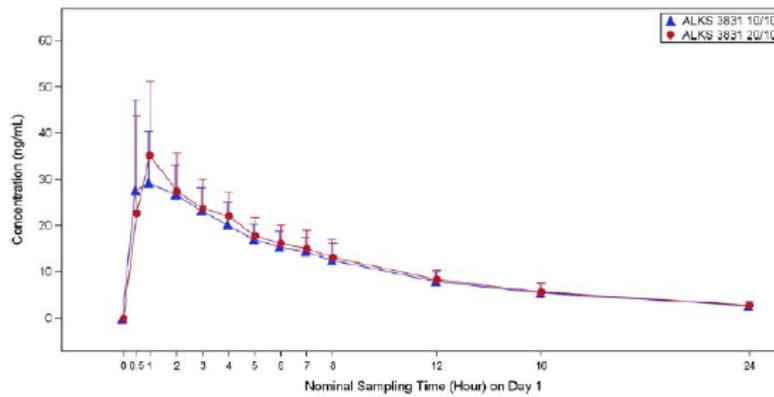
**Figure 11: Plasma Concentrations (Mean +Standard Deviation) of Olanzapine at steady-state on Day 14**



Abbreviation: LLOQ=lower limit of quantification.  
 Note: Values below the LLOQ were set to zero in the calculation of the summary statistics.

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Page 26

**Figure 12: Plasma Concentrations (Mean + Standard Deviation) of Samidorphan on Day 1 and Day 14 (at steady-state)**



Abbreviation: LLOQ=lower limit of quantification.  
 Note: Values below the LLOQ were set to zero in the calculation of the summary statistics.

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Page 27

### 3.3.8 Were there any QT increases observed at highest therapeutic dose levels or supra-therapeutic levels?

No, ALKS 3831 did not have any clinically relevant effect on ECG parameters, including QT interval, at highest therapeutic dose (20/10) or at supratherapeutic doses (30/30).

The effect of samidorphan and olanzapine combination was evaluated in Study # ALK33-A109. This was a randomized, placebo- and positive -controlled, double-blind study with a nested crossover design (moxifloxacin/placebo comparison). The highest dose evaluated was a combination of 30 mg olanzapine and 30 mg samidorphan, which is the maximum tolerated dose for olanzapine (30 mg) and adequately covers the worst case exposure scenario for samidorphan (CYP3A inhibition). ALKS 3831 at supratherapeutic doses (up to 30/30) and plasma concentrations did not have a clinically relevant effect on ECG parameters, including QT interval. The upper bound of the 90% confidence interval (CI) of the predicted placebo-corrected change from baseline in corrected QT interval using Fridericia's formula ( $\Delta\Delta QTcF$ ) did not exceed 10 msec at any of the geometric mean peak concentrations of OLZ or SAM across the dose range evaluated (10/10, 20/20, and 30/30).

**Table 4: The Point Estimates and the 90% CIs (FDA Analysis)**

ECG parameter	Treatment (olanzapine mg/ samidorphan mg)	Concentration (ng/mL)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
QTc	ALKS 3831 10/10	27.2	3.4	(1.3 to 5.5)
QTc	ALKS 3831 20/20	62.3	3.5	(1.0 to 6.0)
QTc	ALKS 3831 30/30	73.3	3.5	(0.8 to 6.3)

Source: FDA IRT- QT study report, NDA 213378/IND 114375- DARRTS, Girish Bende et. al., 11/26/19.

Additionally, exposure-response analysis was also performed between plasma concentrations of olanzapine and samidorphan with  $\Delta\Delta QTcF$  as the dependent variable. The predicted  $\Delta\Delta QTcF$  at the geometric mean peak samidorphan concentrations for the dose of 30/30 on Day 13 were 1.38 (-3.37, 6.12) ms. The predicted  $\Delta\Delta QTcF$  at the geometric mean peak olanzapine concentrations for the dose of 30/30 on Day 13 were 2.33 (-2.72, 7.38) ms. A clinically relevant effect on  $\Delta\Delta QTcF$  (i.e.,  $\geq 10$  msec) can be excluded within the observed range of olanzapine and samidorphan plasma concentrations and up to concentrations of  $\sim 110$  ng/mL and  $\sim 160$  ng/mL, respectively.

## 4. APPENDICES

### 4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods were developed and validated, following the US FDA guideline (Center for Drug Evaluation and Research 2001), for the quantification of OLZ, SAM, and two metabolites of SAM (RDC-9986 and RDC-1066) in human plasma and urine, utilizing LC-MS/MS analysis. All of these validated methods met the performance acceptance criteria in the guidance.

#### Bioanalysis in Plasma

Validation results demonstrated each method to be sensitive, selective, accurate, and reproducible. Stability of the analytes was demonstrated on long-term storage and all study samples were analyzed within validated long-term stability.

#### Bioanalysis in Urine

Validation results demonstrated each method to be sensitive, selective, accurate, and reproducible. Stability of the analytes was demonstrated on long-term storage and all study samples were analyzed within validated long-term stability.

Table 5 Overview of plasma LC-MS/MS Method

APPEARS THIS WAY ON ORIGINAL

Analytical Laboratory	Analyte(s)	LLOQ (ng/mL)	ULOQ (ng/mL)	Validation Report Number
(b) (4)	OLZ, SAM, RDC-9986	0.250	100	AV-0313-20 (Addendum 4)
	SAM, RDC-9986	0.250	100	AV-0313-13 (Amendment 5, Addendum 1)
	SAM, RDC-9986	0.250	100	AV-0313-22
	SAM	0.250	100	AV-0313-05
	RDC-1066	0.250	125	AV-0313-29 (Addendum 1)
	OLZ	0.100	50.0	ABV-1083-01
	Valproic acid	2.00	100,000	2100-772 (Addendum 1)
	Lithium	20	10,000	185085ASVQ
	Moxifloxacin	25.0	5000	8225508 (Addendum 3)

Abbreviations: LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLOQ=lower limit of quantification; OLZ=olanzapine; SAM=samidorphan; ULOQ=upper limit of quantification.

Source: Summary of Biopharmaceutical studies and analytical methods, Page 17

## 4.2 Pharmacometrics Review

### 4.2.1 Executive Summary

Alkermes Inc is seeking an approval for LYBALVI (Olanzapine/Samidorphan) tablets for the treatment of schizophrenia and bipolar I disorder in adults. The recommended dose of LYBALVI is 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg orally.

This document is a review of the sponsor's population pharmacokinetic (Pop PK) analysis which supports labeling statements.

### 4.2.2 Sponsor's Analysis

#### Objectives

- To develop Pop PK models for olanzapine and samidorphan to describe the plasma concentration versus time profiles of each drug after oral administration
- To identify covariates that contribute to inter-subject variability in the PK parameters of both drugs.

#### Data

The PK data from a total of 10 studies with ALKS 3831 (9 phase 1 studies [ALK33-301, ALK3831-A101, -A103, -A104, -A105, A106, -A107, -A109, -B101] and 1 phase 3 study [ALK3831-A305]) were used to develop Pop PK models for olanzapine and samidorphan. Data from one additional phase 1 study with samidorphan alone (ALK3831-B109) was also included in the final Pop PK model for samidorphan.

#### Method

Nonlinear mixed effect modeling was used for PK model development. A base model was first developed to describe olanzapine and samidorphan PK profile. The full model with backwards deletion approach was utilized for covariate modeling. The relationship of continuous covariates and PK parameter was described with power models; and categorical covariate-PK parameter relationship was described with linear models. The final population PK model and its parameter estimates were used to assess the impact of model covariates on steady-state exposures.

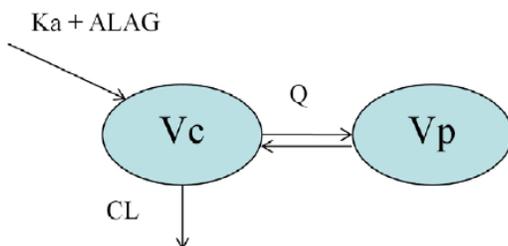
#### Results

##### *Olanzapine:*

The PK of olanzapine was described by 2-compartment model with first-order absorption and elimination and a lag-time for absorption (**Figure 13**). Covariates such as weight, rifampin (concomitant medication), smoking, moderate hepatic impairment, severe renal impairment, race, and gender were added on clearance. Covariates such as weight, and age were added on the

volume of distribution, food effect was added on bioavailability. The parameter estimates of the final population PK model are shown in **Table 6**.

*Figure 13: Schematic of sponsor's final population PK model for olanzapine and samidorphan*



$K_a$ : absorption rate;  $V_c/F$  and  $V_p/F$ : apparent central and peripheral volumes of distribution respectively;  $CL/F$ : apparent clearance;  $Q/F$ : inter-compartmental clearance;  $ALAG$ : dosing lag-time.

Source: Alkermes Report Number: ALK3831-PopPK, Page-60, Figure 4-1

*Table 6: Parameter estimates of sponsor's final population PK model for olanzapine*

Parameter [Units]	NONMEM Estimates			CV% <sup>^</sup>
	Estimate	%RSE	95% CI	
CL/F (L/h)	15.5	2.85	14.6, 16.4	
V <sub>c</sub> /F (L)	656	2.23	627, 685	
K <sub>a</sub> (h <sup>-1</sup> )	0.861	5.70	0.765, 0.957	
ALAG (hr) <sup>[2]</sup>	0.782 Fixed	-	-	
V <sub>p</sub> /F (L)	225	9.42	183, 267	
Q/F (L/hr)	6.15	18.4	3.94, 8.36	
WT ON CL/F <sup>[1]</sup>	0.75 Fixed	-	-	
WT ON V <sub>c</sub> /F <sup>[1]</sup>	1.0 Fixed	-	-	
Inducer Effect of Rifampin in A103 on CL/F	1.80	4.45	1.64, 1.96	
Smoking on CL/F	1.30	3.64	1.21, 1.39	
Food on F	0.943	2.26	0.901, 0.985	
Age on V <sub>c</sub> /F	0.356	11.8	0.273, 0.439	
Moderate Hepatic Impairment on CL/F in Study -A105 <sup>[2]</sup>	0.875 Fixed	-	-	
Severe Renal Impairment on CL/F in Study -A106	0.801	5.67	0.712, 0.890	
Race (Black vs. Non-Black) on CL/F	1.10	3.22	1.03, 1.17	
Gender (Female vs. Male) on CL/F	0.862	3.56	0.802, 0.922	
<b>Inter-individual variability</b>	<b>Estimate</b>	<b>%RSE</b>	<b>95% CI</b>	<b>CV%<sup>^</sup></b>
CL/F	0.171	10.0	0.137, 0.205	43.2
Correlation CL/F & V <sub>c</sub> /F	0.0959	16.4	0.0651, 0.127	0.651
V <sub>c</sub> /F	0.127	17.5	0.0835, 0.171	35.6
Correlation CL/F & K <sub>a</sub>	-0.0291	91.8	-0.0814, 0.0232	-0.154
Correlation V <sub>c</sub> /F & K <sub>a</sub>	0.0384	85.9	-0.0263, 0.103	0.236
K <sub>a</sub>	0.209	50.2	0.00320, 0.415	48.2
Correlation CL/F & ALAG	0.0581	31.0	0.0228, 0.0934	0.249
Correlation V <sub>c</sub> /F & ALAG	0.102	16.5	0.0691, 0.135	0.507
Correlation K <sub>a</sub> & ALAG	-0.0767	49.5	-0.151, -0.00222	-0.297
ALAG	0.319	9.53	0.259, 0.379	61.3
V <sub>p</sub> /F	0.223 Fixed	-	-	50.0
Q/F	0.223 Fixed	-	-	50.0
<b>Inter-occasion variability</b>	<b>Estimate</b>	<b>%RSE</b>	<b>95% CI</b>	<b>CV%</b>
K <sub>a</sub>	0.630	14.2	0.455, 0.805	93.7
<b>Residual variability</b>	<b>Estimate</b>	<b>%RSE</b>	<b>95% CI</b>	<b>CV%</b>
σ <sup>2</sup> <sub>prop</sub>	0.0462	6.26	0.0405, 0.0519	21.5
σ <sup>2</sup> <sub>prop</sub> Study -A305	0.0797	19.6	0.0491, 0.110	28.2

<sup>[1]</sup> Fixed at allometric exponent

<sup>[2]</sup> Fixed at estimate from previous stable model where effect reliably estimated.

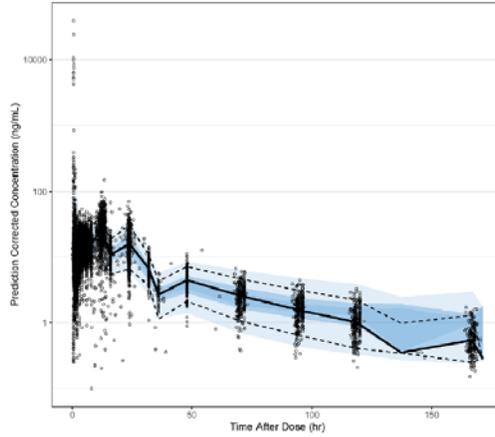
<sup>^</sup> For off-diagonal terms correlation coefficients presented.

Note: Where estimate >0.15 CV calculated as  $CV_{TR} = \sqrt{e^{\omega_p^2} - 1} * 100$  rather than square root of  $\omega_p^2 * 100$

Source: Alkermes Report Number: ALK3831-PopPK, Page-73, Table 4-12

The population PK model for olanzapine was assessed with diagnostics plots including goodness-of-fit (**Figure 20**) and visual predictive checks (VPC) (**Figure 14**). Overall, goodness-of-fit plots and VPC plots adequately describe the PK data of olanzapine. The effect of the covariates on the simulated steady-state PK parameters i.e. C<sub>max,ss</sub> and AUC<sub>tau</sub> of olanzapine is shown in **Figure 15** and **Figure 16**.

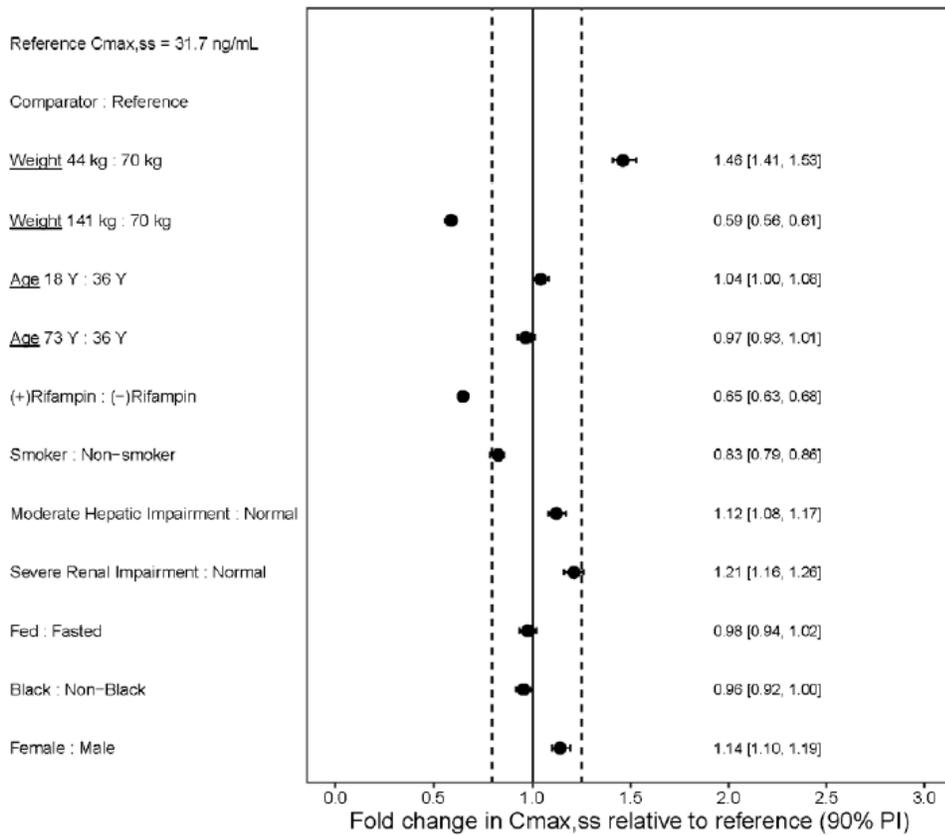
**Figure 14: Prediction-correction VPCs for the final olanzapine population PK model**



Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 5<sup>th</sup> and 95<sup>th</sup> percentile of observed concentrations; Dark Blue Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Light Blue Shaded Region: 95% Prediction Intervals for the 5<sup>th</sup> and 95<sup>th</sup> percentiles of Predicted Concentrations.

Source: Alkermes Report Number: ALK3831-PopPK, Page-688, section 8.10.3

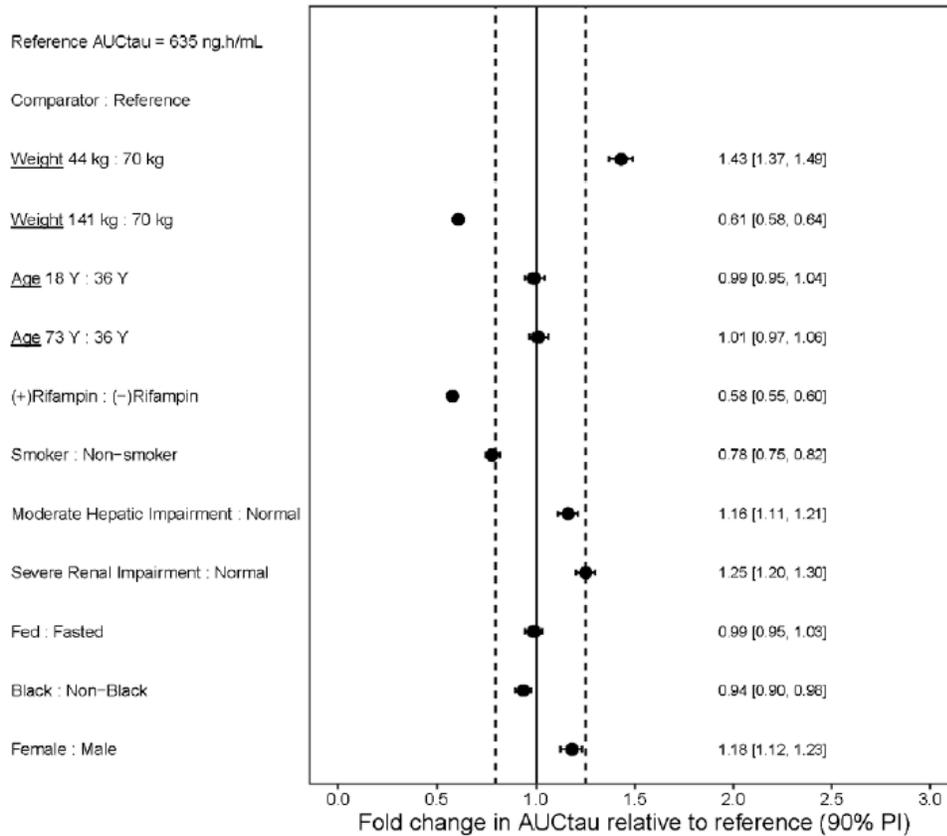
Figure 15: Forest plot of covariate effect in final olanzapine model on simulated  $C_{max,ss}$



Note: Solid vertical line represents no impact of the covariate with the reference subject set as a healthy 36 years old, 70 kg, non-black male non-smoker, with normal hepatic and renal function receiving a once daily oral doses of ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) in a fasted condition. Dashed vertical lines are at 0.8 and 1.25 fold of this value.

Source: Alkermes Report Number: ALK3831-PopPK, Page-77, Figure 4-3

**Figure 16: Forest plot of covariate effect in final olanzapine model on simulated  $AUC_{tau}$**



Note: Solid vertical line represents no impact of the covariate with the reference subject set as a healthy 36 years old, 70 kg, non-black male non-smoker, with normal hepatic and renal function receiving a once daily oral doses of ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) in a fasted condition. Dashed vertical lines are at 0.8 and 1.25 fold of this value.

Source: Alkermes Report Number: ALK3831-PopPK, Page-78, Figure 4-4

### *Samidorphan:*

The PK of samidorphan was described by 2-compartment model with first-order absorption and elimination and a lag-time for absorption (**Figure 13**). Covariates such as weight, rifampin (concomitant medication), moderate hepatic impairment and severe renal impairment were added on clearance. Covariates such as weight were added on the volume of distribution, food effect was added on bioavailability, and formulation were added on absorption lag-time. The parameter estimates of the final population PK model are shown in **Table 7**.

**Table 7: Parameter estimates of sponsor's final samidorphan population PK**

Parameter [Units]	NONMEM Estimates			
	Estimate	%RSE	95% CI	
CL/F (L/h)	35.4	1.65	34.3, 36.5	
V <sub>c</sub> /F (L)	297	1.63	288, 306	
V <sub>p</sub> /F (L)	124	8.87	102, 146	
K <sub>a</sub> (h <sup>-1</sup> )	6.61	14.2	4.77, 8.45	
ALAG (hr)	0.323	5.57	0.288, 0.358	
Q/F (L/hr)	12.1	7.89	10.2, 14.0	
WT ON CL/F <sup>[1]</sup>	0.75 Fixed	-	-	
WT ON V <sub>c</sub> /F <sup>[1]</sup>	1.0 Fixed	-	-	
Inducer Effect of Rifampin in A103 on CL/F	2.70	3.06	2.54, 2.86	
Moderate Hepatic Impairment on CL/F in Study -A105	0.810	9.04	0.667, 0.953	
Severe Renal Impairment on CL/F in Study -A106	0.570	5.96	0.503, 0.637	
Food on K <sub>a</sub>	0.107	36.9	0.0296, 0.184	
Change in ALAG for Study -A305 <sup>[2]</sup>	10.1	11.0	7.92, 12.3	
Formulation (SAM Tablet vs. OLZ/SAM Bilayer Tablet) on ALAG	1.41	5.80	1.25, 1.57	
<b>Inter-individual variability</b>	<b>Estimate</b>	<b>%RSE</b>	<b>95% CI</b>	<b>CV%<sup>^</sup></b>
CL/F	0.0865	11.9	0.0663, 0.107	29.4
Correlation CL/F & V <sub>c</sub> /F	0.0493	20.2	0.0298, 0.0688	0.719
V <sub>c</sub> /F	0.0543	19.0	0.0341, 0.0745	23.3
Correlation CL/F & V <sub>p</sub> /F	-0.116	21.0	-0.164, 0.0682	-0.478
Correlation V <sub>c</sub> /F & V <sub>p</sub> /F	-0.0148	120	-0.0497, 0.0201	-0.0770
V <sub>p</sub> /F	0.681	24.5	0.354, 1.01	98.8
Correlation CL/F & K <sub>a</sub>	-0.00705	359	-0.0566, 0.0425	-0.0181
Correlation V <sub>c</sub> /F & K <sub>a</sub>	-0.0903	25.2	-0.135, -0.456	-0.292
Correlation V <sub>p</sub> /F & K <sub>a</sub>	0.204	77.0	-0.104, 0.512	0.186
K <sub>a</sub>	1.76	16.8	1.18, 2.34	219
Correlation CL/F & ALAG	-0.00134	563	-0.0161, 0.0135	-0.0126
Correlation V <sub>c</sub> /F & ALAG	0.0207	36.6	0.00584, 0.0356	0.245
Correlation V <sub>p</sub> /F & ALAG	0.00795	501	-0.0701, 0.0860	0.0266
Correlation K <sub>a</sub> & ALAG	-0.146	34.9	-0.246, -0.0460	-0.304
ALAG	0.131	24.8	0.0673, 0.195	36.2
Q/F	0.223 Fixed	-	-	50.0
<b>Residual variability</b>	<b>Estimate</b>	<b>%RSE</b>	<b>95% CI</b>	<b>CV%</b>
σ <sup>2</sup> <sub>prop</sub>	0.0610	6.87	0.0528, 0.0692	24.7
σ <sup>2</sup> <sub>prop Study -A305</sub>	0.118	16.9	0.0788, 0.157	34.4

<sup>[1]</sup> Fixed at allometric exponent. <sup>[2]</sup> Dose time not recorded for this study so imputed.

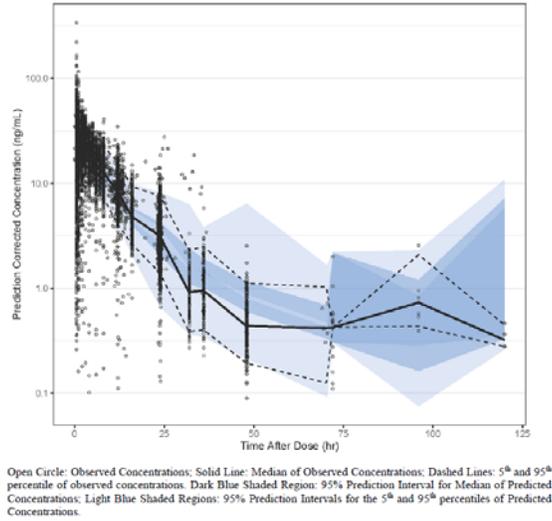
<sup>^</sup> For off-diagonal terms correlation coefficients presented.

Note: Where estimate >0.15 CV calculated as  $CV_{TV} = \sqrt{e^{\omega_p^2} - 1} * 100$  rather than square root of  $\omega_p^2 * 100$

**Source:** Alkermes Report Number: ALK3831-PopPK, Page-103, Table 4-26

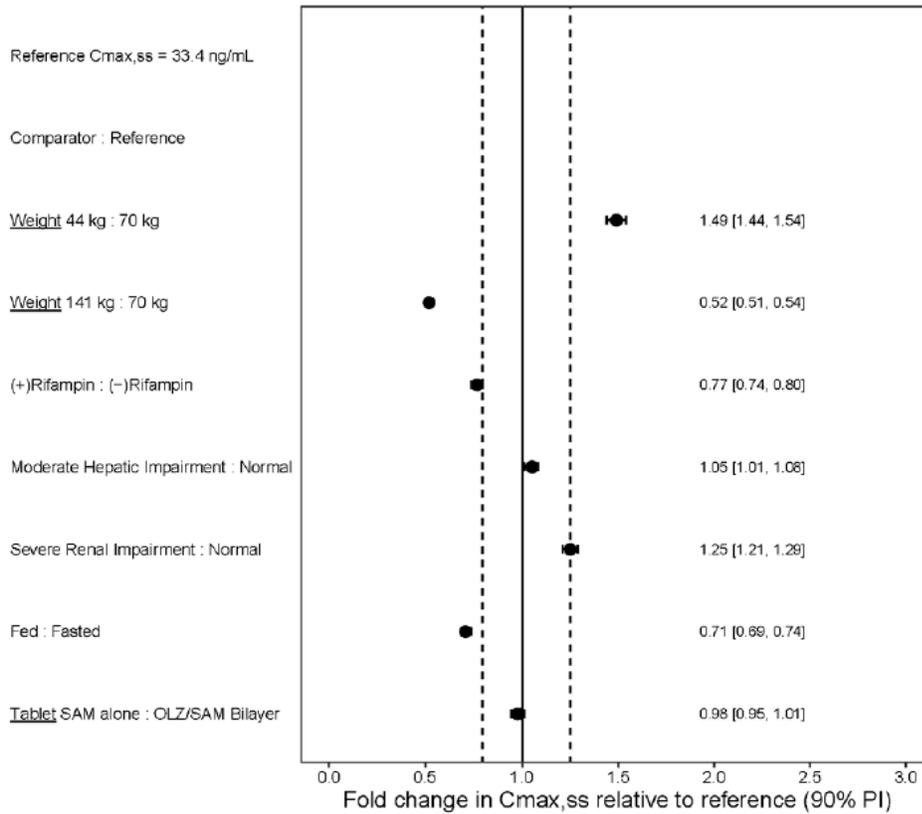
The population PK model for samidorphan was assessed with diagnostics plots including goodness-of-fit (**Figure 21**) and visual predictive checks (VPC) (**Figure 17**). Overall, goodness-of-fit plots and VPC plots adequately describe the PK data of samidorphan. The effect of the covariates on the simulated steady-state PK parameters i.e. C<sub>max,ss</sub> and AUC<sub>tau</sub> of samidorphan is shown in **Figure 18** and **Figure 19**.

**Figure 17: Prediction-correction VPCs for the final population PK model of samidorphan**



**Source:** Alkermes Report Number: ALK3831-PopPK, Page-703, section 8.11.3

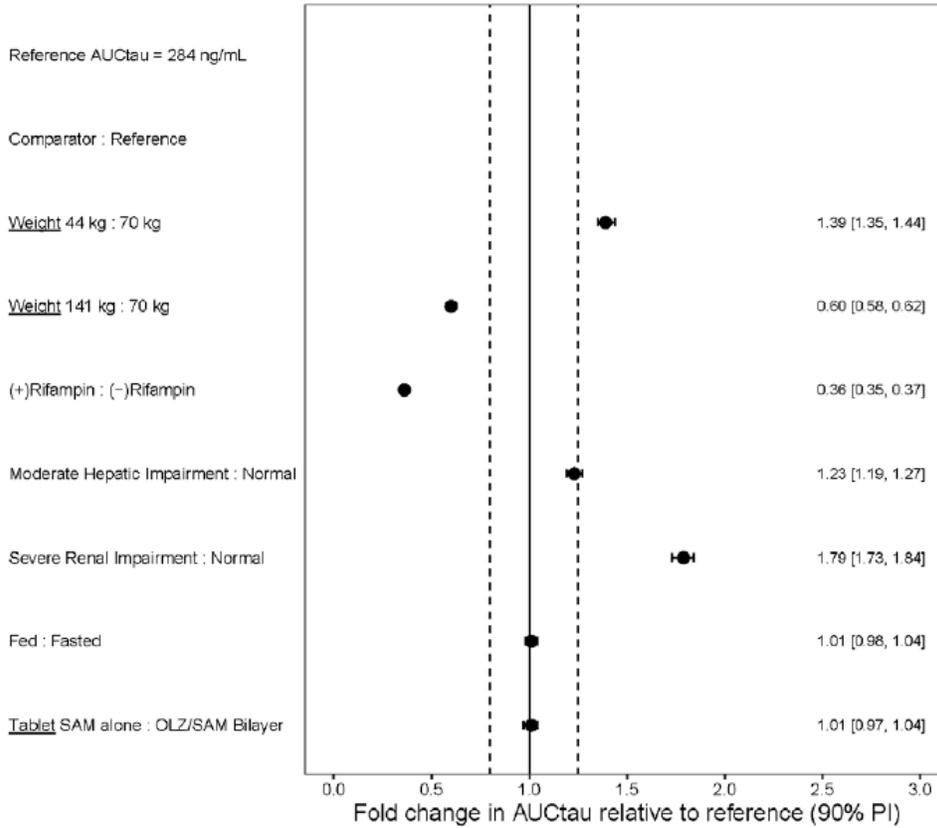
**Figure 18: Forest plot of covariate effect in final samidorphan model on simulated  $C_{max,ss}$**



Note: Solid vertical line represents no impact of the covariate with the reference subject set as a healthy 36 years old, 70 kg, non-black male non-smoker, with normal hepatic and renal function receiving a once daily oral doses of ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) in a fasted condition. Dashed vertical lines are at 0.8 and 1.25 fold of this value.

**Source:** Alkermes Report Number: ALK3831-PopPK, Page-107, Figure 4-6

**Figure 19: Forest plot of covariate effect in final samidorphan model on simulated  $AUC_{tau}$**



Note: Solid vertical line represents no impact of the covariate with the reference subject set as a healthy 36 years old, 70 kg, non-black male non-smoker, with normal hepatic and renal function receiving a once daily oral doses of ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) in a fasted condition. Dashed vertical lines are at 0.8 and 1.25 fold of this value.

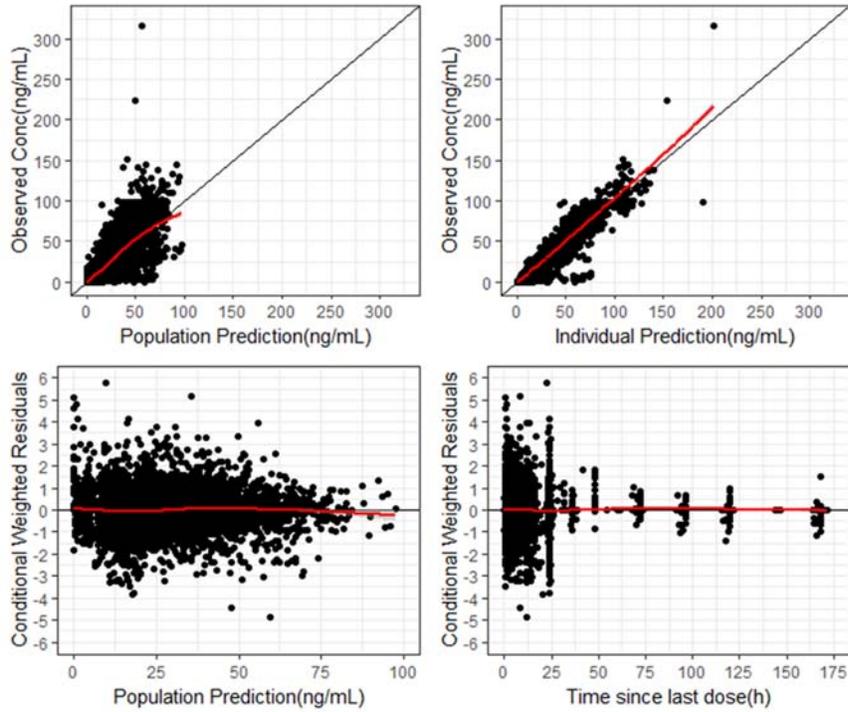
Source: Alkermes Report Number: ALK3831-PopPK, Page-108, Figure 4-7

### 4.2.3 Reviewer's Analysis

#### Sponsor's Pop PK model evaluation

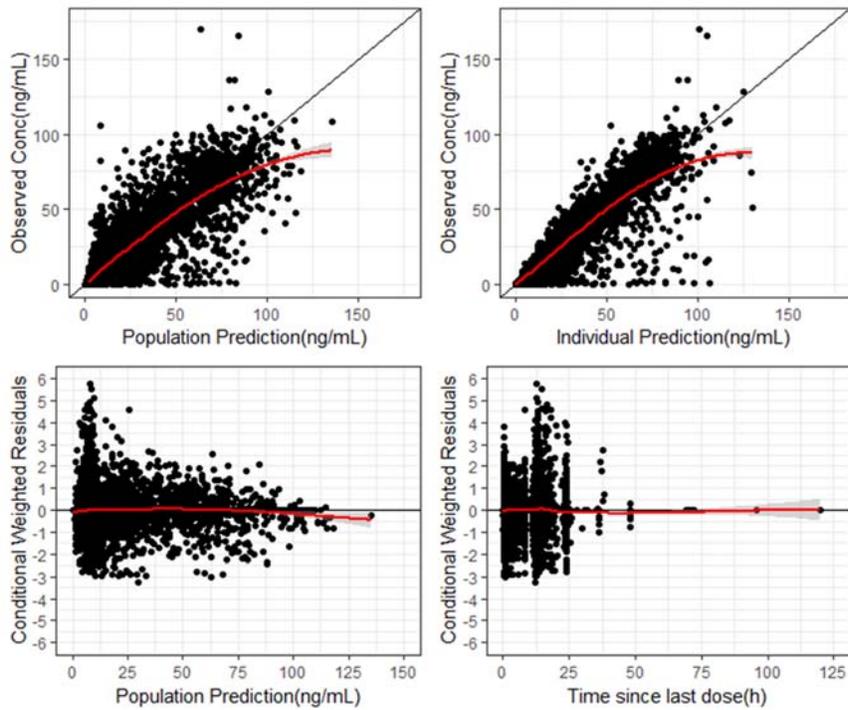
The reviewer was able to run the sponsor's final PK model and obtained similar results as reported by the sponsor. Model diagnostics for olanzapine and samidorphan are shown in **Figure 20** and **Figure 21** respectively.

**Figure 20: General goodness-of-fit plots for olanzapine**



Source: M:\Olanzapine\_samidorpham\_NDA213378\_VS\Reviewer\Rsceipts\pk\_analysis\_olz.R

Figure 21: General goodness-of-fit plots for samidorphan



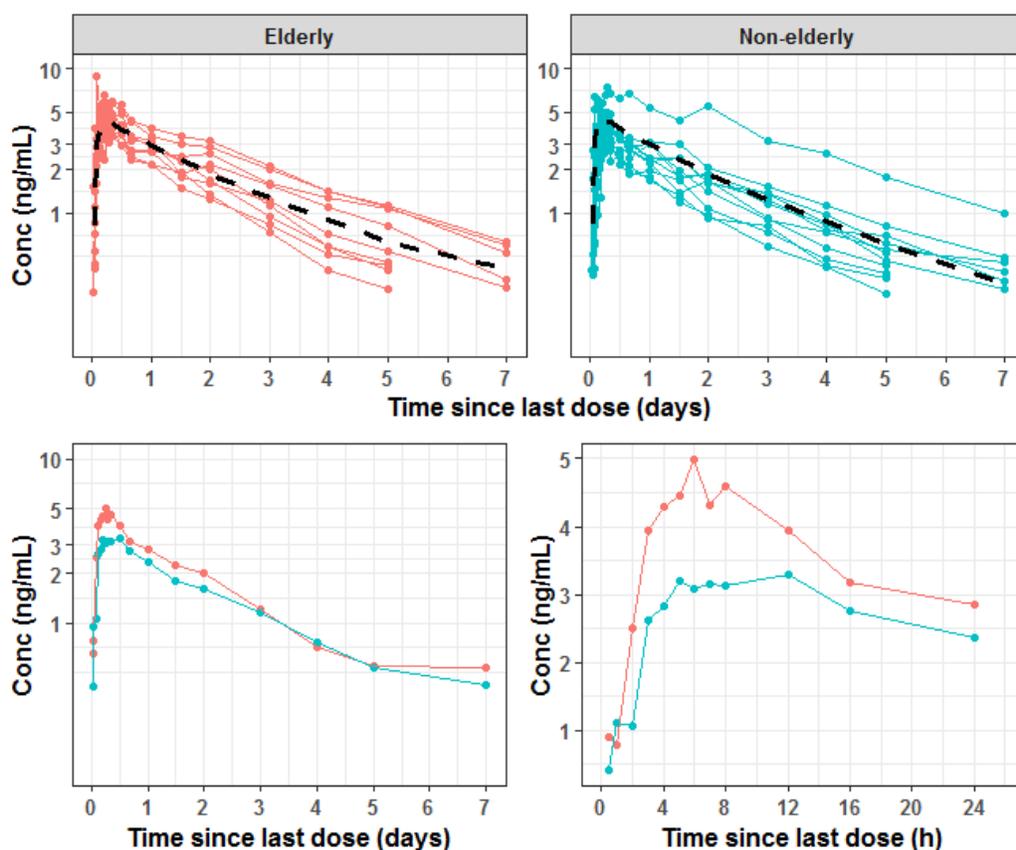
Source: M:\Olanzapine\_samidorpham\_NDA213378\_VS\Reviewer\Rsceipts\pk\_analysis\_sam.R

The PK data was pooled from all studies to evaluate the covariate impact. Subjects from cross-over studies have contributed more than one PK profile in the analysis.

## Age effect

*Olanzapine*: Healthy subjects data from clinical study ALK3831-A105 (hepatic impairment study) and ALK3831-A106 (renal impairment study) suggested ~14% increase in  $C_{max}$  and ~3% increase in  $AUC_{0-\infty}$  for elderly (N=9;  $\geq 65$  years) subjects as compared to non-elderly (N=11;  $< 65$  years) subjects after the first dose of the drug (**Figure 22**).

**Figure 22: Top row: Individual PK profiles of olanzapine by age category. Black dashed line indicates population predictions from sponsor's final PK model; Middle row: Median PK profiles of olanzapine by age category focusing on overall PK profile (left figure) and initial absorption phase (right figure); Bottom row: Summary table of PK parameters of olanzapine from non-compartmental analysis by age category. Red color indicates elderly and strong cyan color indicates non-elderly subjects**



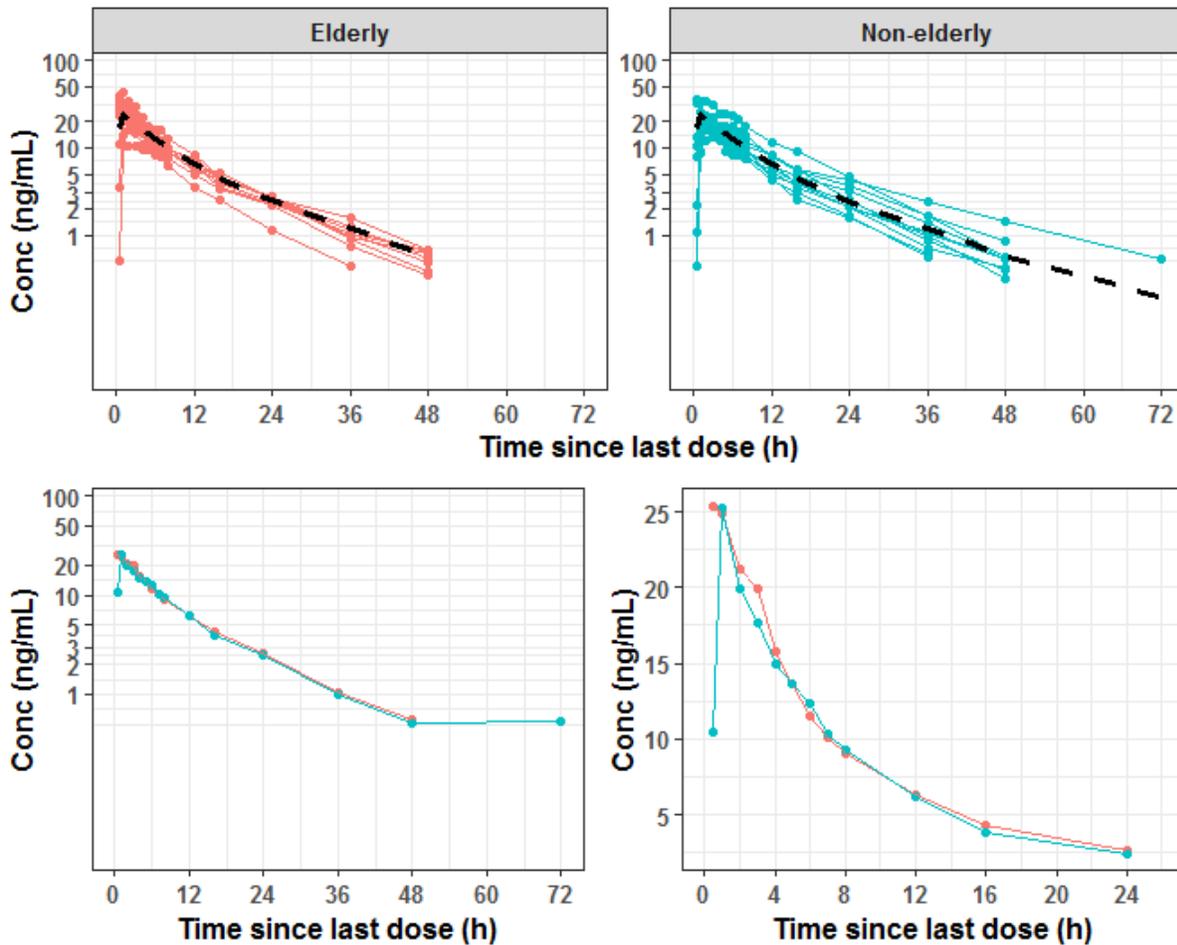
Group	$C_{max}$	$T_{max}$	$AUC_{last}$	$AUC_{inf}$	Half-life	N
Elderly	5.5	5	212.7	234.2	45.1	9
Non-elderly	4.8	7	207.9	226.7	48.0	11

Source: M:\Olanzapine\_samidorpham\_NDA213378\_VS\Reviewer\Rscripts\pk\_analysis\_olz.R

*Samidorphan*: Healthy subjects data from clinical study ALK3831-A105 (hepatic impairment study) and ALK3831-A106 (renal impairment study) suggested similar PK profiles for elderly

(N=9; ≥65 years) subjects and non-elderly (N=11; <65 years) subjects (*Figure 23*), and thus did not suggest any impact of age on the PK of samidorphan.

*Figure 23: Top row: Individual PK profiles of samidorphan by age category. Black dashed line indicates population predictions from sponsor’s final PK model; Middle row: Median PK profiles of samidorphan by age category focusing on overall PK profile (left figure) and initial absorption phase (right figure); Bottom row: Summary table of PK parameters from non-compartmental analysis of samidorphan by age category. Red color indicates elderly and strong cyan color indicates non-elderly subjects*

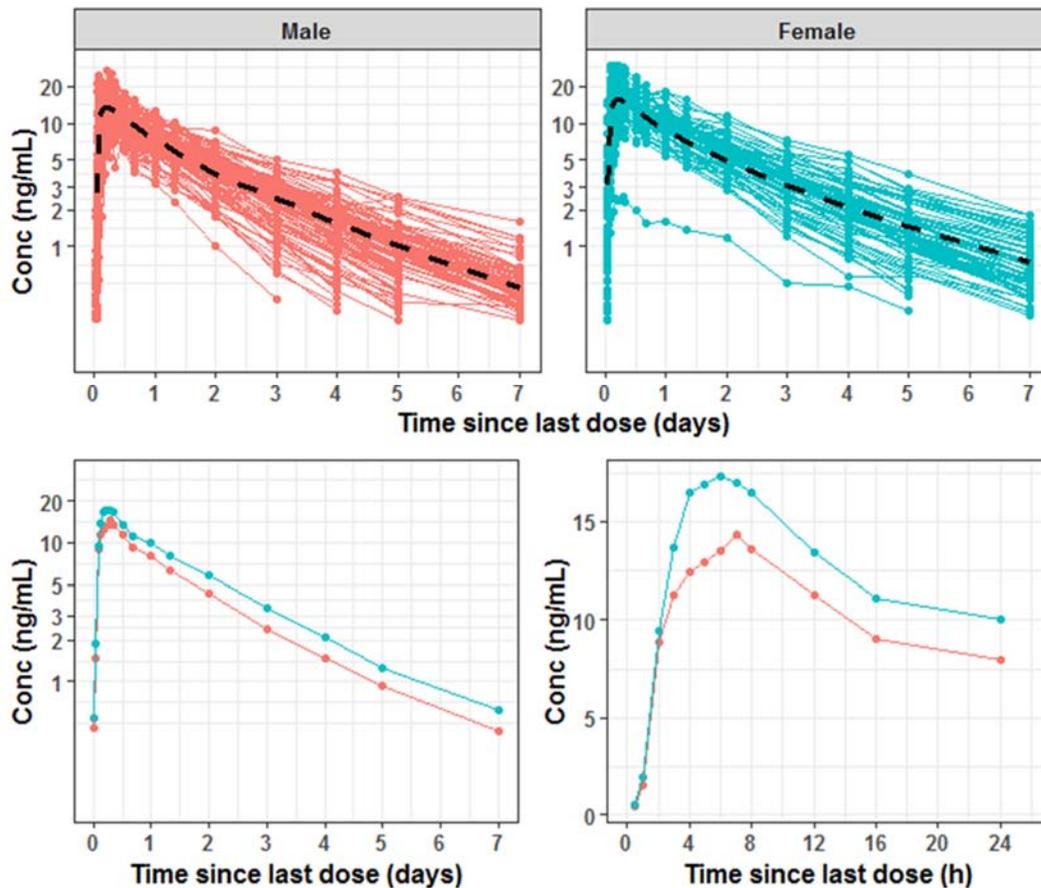


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## Sex effect

*Olanzapine*: Data was pooled from 5 clinical studies to compare the PK profiles of 76 female and 116 male subjects (**Figure 24**). The PK profiles from females show ~19% increase in  $C_{max}$  and ~30% increase in  $AUC_{0-\infty}$  as compared to male subjects after the first dose of the drug.

**Figure 24:** Top row: Individual PK profiles of olanzapine by sex. Black dashed line indicates population predictions from sponsor's final PK model; Middle row: Median PK profiles of olanzapine by sex focusing on overall PK profile (left figure) and initial absorption phase (right figure); Bottom row: Summary table of PK parameters of olanzapine by sex from non-compartmental analysis. Red color indicates male and strong cyan color indicates female subjects

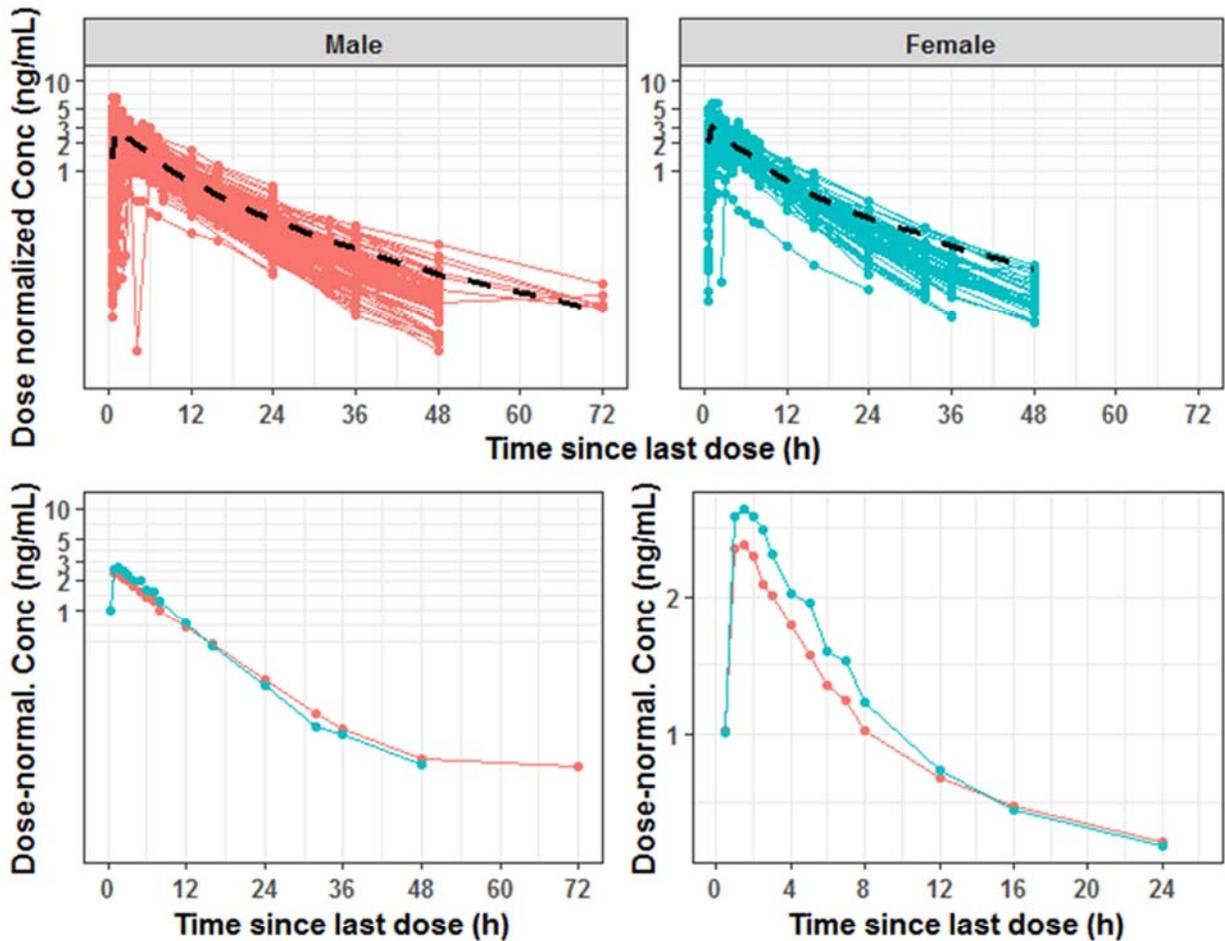


Group	$C_{max}$	$T_{max}$	$AUC_{last}$	$AUC_{inf}$	Half-life	N
Male	15.5	6.0	573.7	596.5	32.8	116
Female	18.5	5.5	733.3	777.4	38.2	76

Source: M:\Olanzapine\_samidorpham\_NDA213378\_VS\Reviewer\Rscripts\pk\_analysis\_olz.R

*Samidorphan*: Data was pooled from 7 clinical studies to compare the PK profiles of 72 female and 223 male subjects (**Figure 25**). The PK profiles of females were similar to the PK profiles of male subjects, and thus did not suggest any impact of sex on the PK of samidorphan.

**Figure 25:** Top row: Individual PK profiles of samidorphan by sex. Black dashed line indicates population predictions from sponsor’s final PK model; Middle row: Median PK profiles of samidorphan by sex focusing on overall PK profile (left figure) and initial absorption phase (right figure); Bottom row: Summary table of PK parameters of samidorphan by sex from non-compartmental analysis. Red color indicates male and strong cyan color indicates female subjects

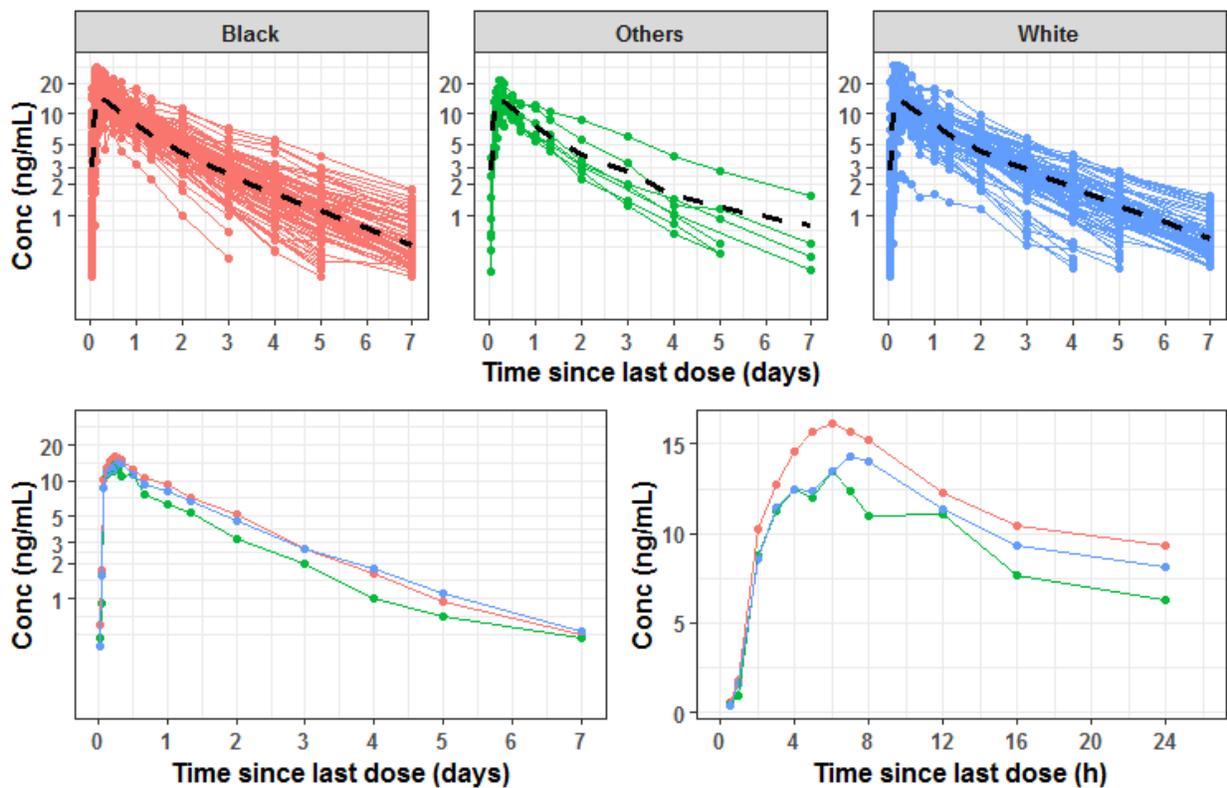


Source: M:\Olanzapine\_samidorphan\_NDA213378\_VS\Reviewer\Rscripts\pk\_analysis\_sam.R

## Race effect

*Olanzapine*: The PK data was pooled from 5 clinical studies to compare the PK profile of 91 White, 94 African-American and 7 other subjects. The PK profiles from black subjects show ~13% increase in  $C_{max}$  and ~4% increase in  $AUC_{0-\infty}$  as compared to white subjects after the first dose of the drug (**Figure 26**). However, the population PK model based on complete dataset have shown ~10% increase in clearance for black subjects as compared to non-black subjects.

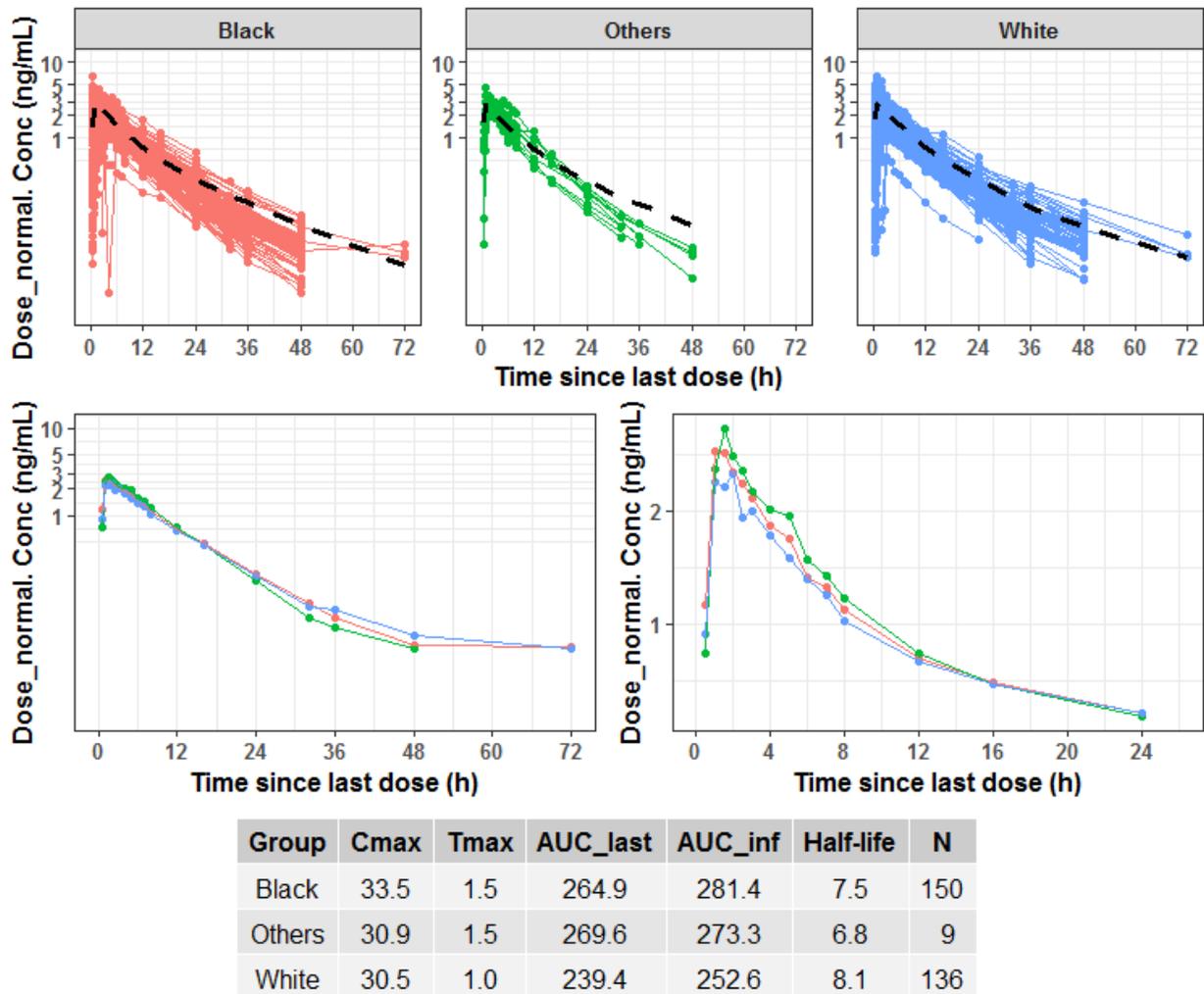
**Figure 26:** Top row: Individual PK profiles of olanzapine by race. Black dashed line indicates population predictions from sponsor's final PK model; Middle row: Median PK profiles of olanzapine by race focusing on overall PK profile (left figure) and initial absorption phase (right figure); Bottom row: Summary table of PK parameters of olanzapine by race from non-compartmental analysis. Red color indicates 'Black', green color indicates 'Others' and dark blue color indicates 'White' subjects.



Source: M:\Olanzapine\_samidorpham\_NDA213378\_VS\Reviewer\Rsceipts\pk\_analysis\_olz.R

*Samidorphan*: The PK data was pooled from 7 clinical studies to compare the PK profile of 136 White, 150 African-American and 9 other subjects. The PK profiles of all races were similar (*Figure 27*), and thus did not suggest any impact of race on the PK of samidorphan.

*Figure 27: Top row: Individual PK profiles of samidorphan by race. Black dashed line indicates population predictions from sponsor’s final PK model; Middle row: Median PK profiles of samidorphan by race focusing on overall PK profile (left figure) and initial absorption phase (right figure); Bottom row: Summary table of PK parameters of samidorphan by race from non-compartmental analysis. Red color indicates ‘Black’, green color indicates ‘Others’ and dark blue color indicates ‘White’ subjects.*

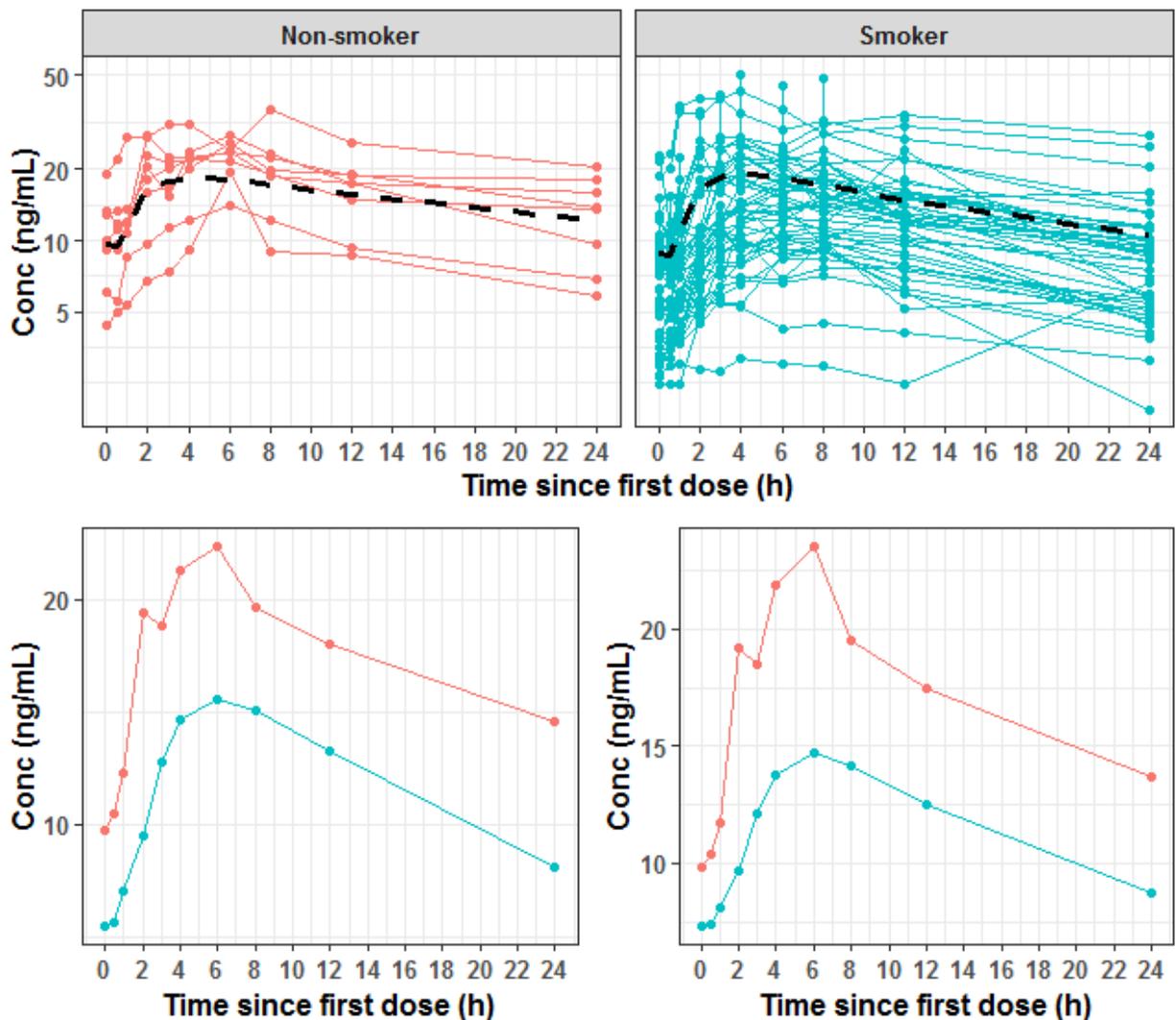


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### Smoking effect

*Olanzapine*: The PK data from clinical study ALK3831-A104 was used to compare the PK profiles of 48 smokers and 8 non-smokers. The PK data of olanzapine for smokers suggest decrease in both  $C_{max}$  and  $AUC_{0-\infty}$  as compared to non-smokers after the first dose of the drug (**Figure 28**). Population estimates have shown 30% increase in clearance for smoker as compared to non-smokers.

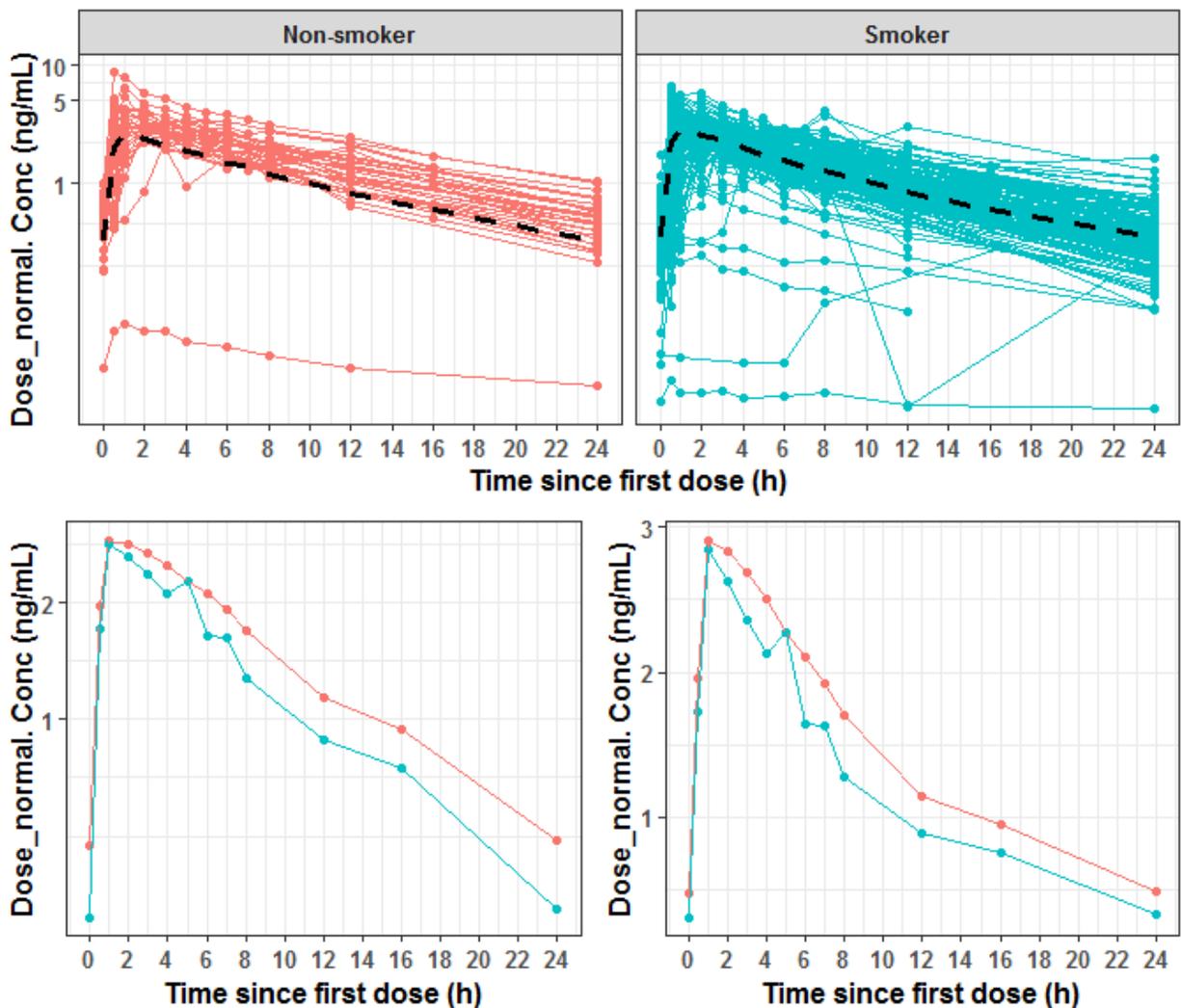
**Figure 28:** Top row: Individual PK profiles of olanzapine by smoking status. Black dashed line indicates population predictions from sponsor's final PK model; Bottom row: Median PK profiles of olanzapine by smoking status focusing on overall PK profile (left figure) and initial absorption phase (right figure). Red color indicates non-smoker and strong cyan color indicates smoker subjects



Source: M:\Olanzapine\_samidorpham\_NDA213378\_VS\Reviewer\Rscripts\pk\_analysis\_olz.R

*Samidorphan*: The PK data from clinical studies ALK3831-A104 and ALK3831-A109 was used to compare the PK profiles of 33 non-smokers and 164 smokers. Population predictions for samidorphan were underpredicted in non-smokers. The PK data of samidorphan for smokers have suggested slight decrease in  $AUC_{0-\infty}$  as compared to non-smokers after the first dose of the drug (**Figure 29**). However, the difference in  $AUC_{0-\infty}$  is not clinically significant considering the data variability.

**Figure 29:** Top row: Individual PK profiles of samidorphan by smoking status. Black dashed line indicates population predictions from sponsor's final PK model; Bottom row: Median PK profiles of samidorphan by smoking status focusing on overall PK profile (left figure) and initial absorption phase (right figure). Red color indicates non-smoker and strong cyan color indicates smoker subjects



Source: M:\Olanzapine\_samidorphan\_NDA213378\_VS\Reviewer\Rscripts\pk\_analysis\_sam.R

#### 4.2.4 Listing of Analysis Codes and Output Files

<b>File Name</b>	<b>Description</b>	<b>Location</b>
pk_analysis_olz.R	Exploratory PK analysis	\\Reviews\ Olanzapine_samidorphan_NDA213378_VS\Reviewer\Rscripts
pk_analysis_sam.R	Exploratory PK analysis	\\Reviews\ Olanzapine_samidorphan_NDA213378_VS\Reviewer\Rscripts

#### 4.2.5 References

1. Alkermes Report Number: ALK3831-PopPK report. Population pharmacokinetic analysis of Olanzapine and Samidorphan when administered in combination as ALKS 3831.

## 4.3 PBPK Review

### 4.3.1 Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to predict the effect of a strong CYP3A inhibitor on samidorphan exposure (AK3831-PBPK-06 report, entitled "Quantitative Prediction of the Effect Of CYP 3A4 and CYP1A2 Inhibition/Induction on Systemic Exposure of Olanzapine and Samidorphan When Administered in Combination by the Oral Route as ALKS 3831" ) and the effects of hepatic impairment on the exposure of orally administered samidorphan ALKS 3831 (AK-3831-PBPK-10 report, entitled "Quantitative Prediction of the Effect of Hepatic Impairment on The Pharmacokinetics of Olanzapine and Samidorphan When Administered in Combination by the Oral Route as ALKS 3831").

The Division of Pharmacometrics has reviewed the original PBPK reports, supporting modeling files, and the Applicant's response to FDA's request for information dated 19 May 2020 to conclude the following:

- The PBPK model of samidorphan is adequate to predict the samidorphan PK profile in healthy volunteers under different dosing levels and administration routes.
- The PBPK model of samidorphan is adequate to assess the effect of hepatic impairment on samidorphan PK profile.
- The model predicted that a strong CYP3A4 inhibitor (such as itraconazole) may increase C<sub>max</sub> and AUC ratios for samidorphan by approximately 1.3 and 1.6-fold, respectively, with concomitant administration of a single oral dose of samidorphan with multiple doses of itraconazole.
- The predicted steady state C<sub>max</sub> and AUC ratios for samidorphan in subjects with moderate HI relative to subjects with normal HF were 1.8 and 2.0, respectively.
- The predicted steady state C<sub>max</sub> and AUC ratios for samidorphan in subjects with severe HI relative to subjects with normal HF were 2.1 and 2.6, respectively.

### 4.3.2 Background

ALKS 3831 (brand name LYBALVI, NDA 213378) is an oral, fixed-dose combination of 10 mg of samidorphan co-formulated with 5 mg, 10 mg, 15 mg or 20 mg of olanzapine. The Applicant's proposed maximum dose is 20 mg/10 mg (olanzapine (OLZ)/samidorphan (SAM)) once daily as a single tablet. The pharmacokinetics (PK) of both OLZ and SAM were linear over the clinical dose range, and there was no PK interaction between OLZ and SAM after oral administration of ALKS 3831 (ALK-3831 Clinical Pharmacology Summary, NDA 213378). This NDA is submitted as 505(b)(2). The Applicant relied on the clinical pharmacology findings of ZYPREXA (olanzapine, NDA 020592) and (b) (4) -with additional clinical studies conducted for ALKS 3831 as required (refer to clinical pharmacology review section).

In this submission, clinical pharmacology data, previously submitted

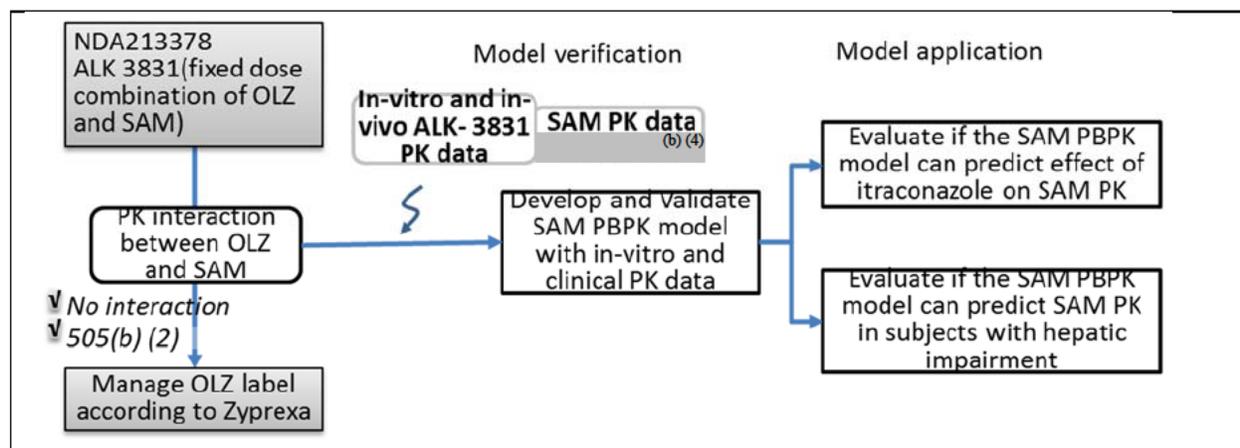
(b) (4)

was used to support the clinical PK of SAM.

(b) (4)

Figure 30 shows a diagram representing the process for identifying the review strategy and specific objectives.

*Figure 30. Decision flowchart for identifying the PBPK review objectives*



Source: Summarized by reviewer

SAM is mainly metabolized by CYP3A4 to its major metabolite, RDC-9986. The human mass balance study (Study ALK33-B107) reported that approximately 17.5% of the total oral dose was excreted unchanged in urine following a single oral dose of 2 mg samidorphan, while a minimal amount of unchanged drug was detected in feces. Applicant reported that the formation of RDC-9986 accounted for approximately 53% of the metabolism of samidorphan (PBPK report #6). The apparent clearances of SAM after oral and sublingual dosage were 51.5 and 47.5 L/h, and renal clearances of 11.0 and 10.6 L/h, respectively (Study ALK33-B107). Following multiple doses of 10 and 20 mg SAM once daily for 7 days in patients, a linear dose-exposure relationship was reported, with minimal accumulation (Study ALK33-003). Based on in-vitro study, both SAM and RDC-9986 are not perpetrators for major CYP enzymes, except for SAM being a weak inhibitor of CYP2C19 (PBPK report #6).

Clinical DDI studies were conducted to evaluate the effect of the strong CYP3A inhibitor itraconazole on SAM PK following a (b) (4) dose of 2 mg SAM (b) (4) and the effect of the strong CYP3A inducer rifampin on SAM PK following a single oral dose of ALKS 3831 10/10 mg (Study ALK3831-A103). Study (b) (4) reported a 1.46-fold increase in samidorphan AUC (b) (4) in the presence of itraconazole. Coadministration with rifampin decreased AUC of SAM by approximately 70% with a single oral administration of ALKS 3831 10/10 (Study ALK3831-A103). The Applicant

also conducted clinical studies (b) (4) and Study ALK3831-A105 (NDA 213378) in hepatic impairment (HI) subjects evaluating the effect of reduced hepatic function on the exposure of SAM administered via (b) (4) oral routes, respectively.

Refer to clinical pharmacology review sections for general clinical pharmacology characteristics of SAM and relevant in-vitro and in-vivo studies.

The objective of this review is to evaluate the adequacy of Applicant’s PBPK analyses in supporting the proposed prescription information (USPI) as shown in **Table 8**:

**Table 8 Applicant’s proposed USPI information related to PBPK modeling**

	<b>Proposed USPI</b>	<b>PBPK Review Objective</b>
<b>Sec 7.2</b>	(b) (4) No PBPK-related language proposed)	Evaluate the effect of itraconazole on the PK of SAM, following administration of ALK-3831
<b>Sec 8.6</b>	(b) (4) (No PBPK-related language proposed)	Evaluate the exposure of SAM following administration of ALK-3831 in subjects with severe hepatic impairment

Source: Applicant’s proposed USPI

#### 4.3.3 Methods

##### Basic PBPK model for SAM

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V17, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The SAM PBPK model was developed based on in-vitro and human ADME studies as well as clinical PK data. Briefly, a first-order absorption model and a minimal PBPK model were utilized to describe SAM PK. The first-order absorption rate ( $k_a$  value = 0.7 1/h) was optimized to recover the observed  $T_{max}$  of approximately 1 hour (Study ALK33-B107). The fraction absorbed ( $f_a$ ) was estimated based on Caco-2 data. In vitro permeability data (Study AM-3831-04AIV0208) under different drug concentrations and pH values was used to estimate the human intestinal effective permeability ( $P_{eff\ human} = 4.6 \times 10^{-4}$  cm/s) value and the hybrid intestinal blood flow parameter ( $Q_{Gut} = 14.8$  L/h). The unbound fraction in enterocytes ( $f_{uGut}$ ) was assumed to be 1.

The in-vitro unbound fraction in plasma ( $f_{up} = 0.69$ ) and in-vivo blood to plasma concentration ratio ( $B/P = 1$ ) values were used in the model. A volume of distribution ( $V_{ss}$ ) of 3.43 L/kg was predicted using “Method 3”<sup>1</sup> within the simulator. This value is comparable with estimates from population PK analysis (4.08 L/kg) for samidorphan following IV administration (Study ALK33-B107).

<sup>1</sup> A refined Rodgers and Rowland method (PMID: 17372687)

In-vitro intrinsic clearance of 11.15  $\mu\text{L}/\text{min}/\text{mg}$  protein was derived from the human liver microsomes study (Study AM-0313-02). In-vitro intrinsic clearance was then scaled to an IV clearance. When this clearance value was combined with a renal clearance (CLR) of 11.0 L/h (Study ALK33-B107), the final total clearance value of 33.1 L/h was consistent with the observed value of 33.7 L/h following IV administration (Study ALK33-B107). Based on the mass balance data (Study ALK33-B107), the contribution of CYP3A pathway is assigned to be 53% of hepatic clearance and 33% to the total clearance. The basic SAM PBPK model was used to simulate the PK of SAM following IV, SL and oral administration. The Applicant assumed that the sublingually administered SAM was 100% absorbed orally.

**Reviewer’s comment:**

- An information request (IR) was sent to the Applicant on 5/19/2020. The Reviewer requested the Applicant to demonstrate the SAM PBPK model could describe the PK of SAM following IV, SL and oral administration as reported in the Study ALK33-B107. The Applicant noted that the inhalation route was used to mimic sublingual administration, where 20% of the dose was assigned to be absorbed via oral mucosa and the remaining was assigned to be absorbed via GI tract. The Reviewer considered this approach acceptable. This modeling approach (20% absorbed via oral mucosa and 80% via GI tract) was used in all PBPK simulations following SL administration in this review.

Simulations were performed using the default healthy volunteer population model (software’s library, V17) and conducted in the fasted state. Default itraconazole fasted solution (and metabolite hydroxy-itraconazole) model files were applied in the simulation.

**Hepatic impairment models for SAM**

The basic PBPK model for SAM (oral tablet and sublingual product) were used to simulate the effect of reduced hepatic function on SAM PK. The Simcyp default population model based on Child-Pugh categories was used to represent subjects with mild (CP-A), moderate (CP-B), and severe (CP-C) HI in the Applicant’s PBPK analyses. The Applicant noted that the HI model predicted an increase in the fup value due to the decreased albumin in HI subjects. Binding of samidorphan to plasma proteins was not measured in the Clinical HI Study ALK3831-A105. Thus, the Applicant conducted two PBPK simulation for HI subjects using the original fup value (0.69) and the predicted fup values for HI subjects.

The following parameter changes were made to the basic model to simulate the effect of HI as summarized in **Table 9**.

**Table 9 Summary of changes in HI models for SAM**

	<b>Virtual HI population (Simcyp cirrhosis model V17)</b>
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<b>Physiological changes in HI relative to HV</b>	<ul style="list-style-type: none"> <li>The decreased liver volume and CYP abundance with increasing severity of HI is based on literature data (Johnson et al., 2010).</li> <li>Albumin, hematocrits, and plasma glycoprotein decreased with increasing severity of HI -&gt; Decreased protein binding</li> <li>30%, 71%, and 86% reduction of hepatic CYP3A4 expression is predicted in subjects with mild, moderate and severe HI</li> <li>Gastric emptying time is 0.3, 0.48, 0.55, 0.6 hour for healthy subjects and subjects with mild, moderate and severe HI</li> </ul>	
	<b>SAM HV model</b>	<b>SAM HI model</b>
	Healthy	Subject with hepatic impairment
<b>Absorption rate (Ka)</b>	0.7 h <sup>-1</sup>	Moderate HI 1.6 h <sup>-1</sup> (PBPK report #10, page 45)
<b>fup</b>	0.69	0.69 or 0.71, 0.76, and 0.81 for mild, moderate, severe HI, respectively (PBPK report #10, table 2)

Source: Summarized by reviewer

### PBPK model verification

The performance of SAM PBPK model in predicting the SAM PK profile in various exposure scenarios was evaluated via the comparison of simulated and observed clinical PK data. **Table 10** presents the summary of the clinical PK, DDI and hepatic impairment studies used for model development and verification. The clinical DDI study with itraconazole (b) (4) was used to verify the contribution of CYP3A4 to the disposition of SAM (b) (4).

For the HI population, the clinical study ALK3831-A105 was used to assess the impact of moderate hepatic impairment on the exposure of samidorphan after a single oral dose of ALKS 3831 5/10 (5 mg olanzapine/10 mg samidorphan).

**Table 10 Summary of the clinical PK, DDI and hepatic impairment studies used for model development and verification**

Study	Mechanism	Formulation	SAM dosing regimen	PBPK Model Objective
ALK33-B107	Clinical PK	SAM only injection	A single IV dose of 2 mg SAM	Model development
ALK33-B107	Clinical PK	SAM only tablet	A single SL dose of 2 mg SAM	Model development
ALK33-B107	Clinical PK	SAM only oral solution	A single oral dose of 2 mg SAM	Model development
ALK33-301	Clinical DDI	SAM only tablet	A single oral dose of 5 mg SAM with/without a single oral dose of 10 mg OLZ	Additional verification by Reviewer
ALK3831-A104	Clinical PK	SAM+OLZ tablet	SAM 10 and 20 mg qd for 5 days	Model verification
(b) (4)	Clinical DDI	(b) (4)	(b) (4)	Model verification

ALK3831-A104	Clinical DDI	SAM + BUP tablet	Rifampin 600 mg qd for 10 days + a single oral dose of SAM 10 mg on day 10	Model verification
ALK3831-A105	Hepatic Impairment	SAM+OLZ tablet	A single oral dose of SAM 10 mg in subjects with moderate HI	Model verification
(b) (4)	Hepatic Impairment	(b) (4)	(b) (4)	Additional verification by Reviewer
	Clinical DDI		Itraconazole 200 mg qd for 5 days + a single oral dose of SAM 10 mg on day 5	Model Application
	Hepatic Impairment		Multiple oral doses of SAM 10 mg in subjects with mild, moderate, and severe HI	Model Application

Source: Summarized by reviewer

**Reviewer's comments:**

- OLZ is mainly metabolized via UGT1A4 and CYP1A2, and is not an inhibitor of the major CYP enzymes including CYP3A4. In contrast, SAM is a substrate of CYP3A4. There is little overlapping on the metabolic mechanisms between these two drugs, and an interaction between them is expected to be low. In addition, results of the clinical study ALK33-301 indicated that the magnitudes of change in the C<sub>max</sub> and AUC of SAM were less than 10% when SAM was co-administered with or without 10 mg OLZ (Table 11).

**Table 11 Observed SAM PK profile in the presence and absence of olanzapine**

Parameters	SAM (5 mg), n=19	SAM (5 mg) + OLZ (10 mg), n=34
AUC <sub>0-24</sub> (ng/mL.h) (GM, CV%)	113.1 (19.1%)	108.5 (22.3%)
C <sub>max</sub> (ng/mL) (GM, CV%)	13.3 (28.5%)	12.9 (28.9)
T <sub>max</sub> (h) (Mean, SD)	3 (1.6)	2.2 (1.2)

Source: Table 16, Study ALK33-301

- SAM PBPK model was able to describe the PK profiles of SAM under different routes of administration, as shown in **Table 12**. In addition, a linear PK of SAM was reported following either (b) (4) (1-16 mg) or oral (5-30) administration (Clinical Pharmacology Summary for (b) (4) and ALK3831). The Reviewer concluded the SAM PBPK model can be used to extrapolate clinical information obtained under different dosing levels and administration routes.

*Table 12 Simulation settings used to predict the PK of SAM following IV, sublingual and oral administration*

Route	IV		Sublingual		Oral		Oral	
Dose	1 mg		2 mg		2 mg		10 mg	
Route setting	IV Bolus		80% and 20% absorbed via GI tract and oral mucosa, respectively		Oral		Oral	
	Obs <sup>1</sup>	Pred/Obs	Obs <sup>1</sup>	Pred/Obs	Obs <sup>1</sup>	Pred/Obs	Obs <sup>2</sup>	Pred/Obs
AUclast (ng/mL.h)	27.7	0.98	41.3	1.03	39.9	1.02	246	0.93
Cmax (ng/mL)	11.2	1.04	4.1	1.27	4.1	1.24	27.8	1.11

Source: Applicant’s response to FDA’s IR dated 5/19/2020, and Table 4 and 7 of PBPK report #6; <sup>1</sup>Observed data: ALK33-B107 <sup>2</sup>Observed data: ALK33-B107

- PBPK modeling can be used as an in-silico testing tool to evaluate the impact of the known physiological difference on the PK of an investigational drug for an intended population. However, the applicability of PBPK modeling to prospectively estimate the effect of hepatic impairment on a drug’s PK has not been fully established. The Applicant’s SAM HI PBPK model was supported with data from the clinical HI study (b) (4). This study evaluated the SAM PK in subjects with mild, moderate, and severe HI compared to HV subjects, following a single (b) (4) dose of SAM.

### **PBPK model application**

The PBPK analyses were applied prospectively to predict the following:

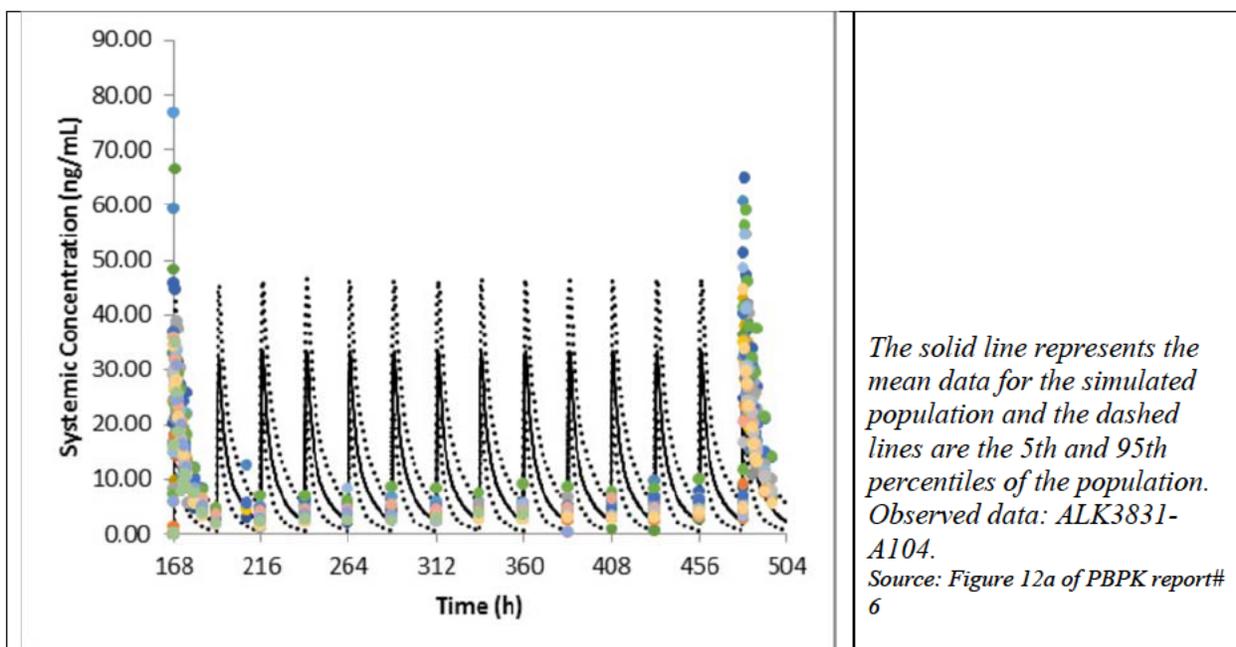
- Effects of itraconazole (strong CYP3A4 inhibitor) on the PK of SAM following a single oral dose of SAM 10 mg
- Samidorphan exposure following multiple oral doses of SAM 10 mg in subjects with mild, moderate and severe HI.

#### **4.3.4 Results**

##### **Q1. Does the PBPK model adequately describe the PK profiles of SAM in various exposure scenarios?**

Yes. PBPK simulations reasonably described SAM PK profile following a single dose of IV, sublingual or oral administration (**Table 12**) in healthy subjects, and multiple-dose of oral administration in patients (**Figure 31**). **Figure 31** present the simulated and observed plasma concentration-time profile of SAM following 14 days of once daily oral doses of ALKS 3831 10/10 in patients with schizophrenia (ALKS 3831 10/10 given on day 7 after 7 days of olanzapine-only treatment).

*Figure 31. Simulated and observed plasma concentration-time profile of samidorphan*



Source: Sponsor PBPK report#6, Fig 12a

**Q2. Can the Applicant’s PBPK models predict the SAM PK profiles when co-administrated with a strong CYP3A inhibitor**

Yes. The Applicant’s SAM PBPK model is adequate to predict the DDI effect of itraconazole on SAM PK following different administration routes. As shown in **Table 13**, the model reasonably described the observed DDI effects of itraconazole on SAM PK following co-administration of multiple doses of itraconazole and a single SL dose of SAM 2 mg in healthy subjects. The model predicted a 1.25- and 1.56-fold increase in the C<sub>max</sub> and AUC of SAM (single oral dose of 10 mg), respectively, with concomitant administration of itraconazole solution (200 mg QD for 5 days).

*Table 13: Predicted and observed ratios for C<sub>max</sub> and AUC of SAM in the presence and absence of itraconazole*

	+ a single SAM 2 mg SL		+ a single SAM 10 mg PO	
	C <sub>max</sub> R	AUC R	C <sub>max</sub> R	AUC R
<b>Predicted</b>	1.22	1.51	1.25	1.56
<b>Observed</b>	1.12	1.5		
<b>P/O</b>	1.12	1.05		

Source: Applicant’s response to FDA’s request for information dated 19 May 2020

**Q3. Can the Applicant’s PBPK models predict the SAM PK profiles following multiple oral doses of SAM 10 mg in subjects with mild, moderate and severe HI**

Simulations using the SAM HI PBPK model reasonably described the SAM PK profiles following a single oral dose of 10 mg SAM in moderate HI population. **Figure 32** compared the simulated and observed plasma-time PK profiles of samidorphan following a single oral dose of ALKS 3831 5/10 (10 mg SAM) in healthy subjects and subjects with moderate hepatic impairment.

*Figure 32 Simulated and observed plasma concentrations of samidorphan following a single oral dose of 10 mg SAM in healthy subjects and subjects with moderate hepatic impairment*

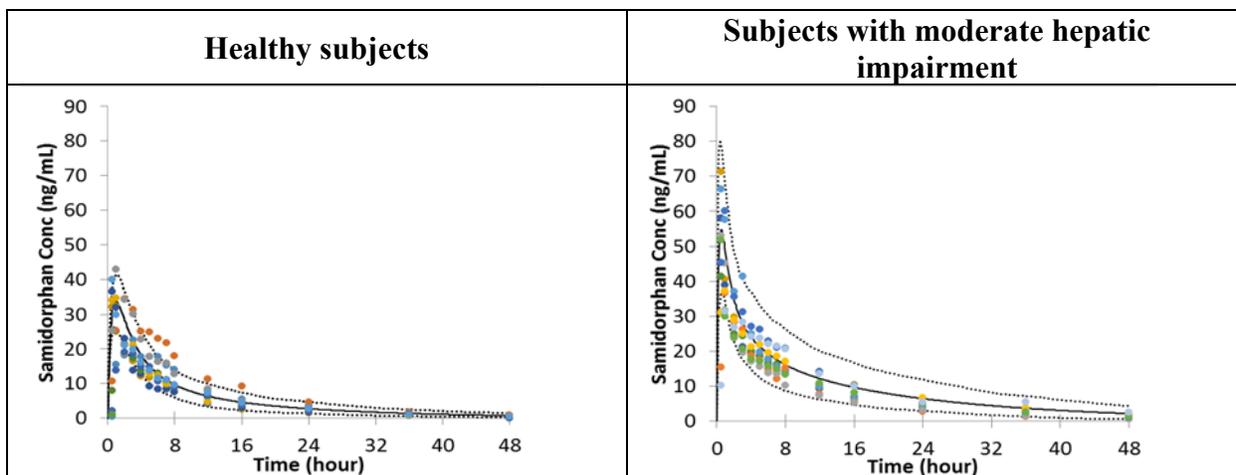


Figure extract from simulation output files: alks3831-5-10-a105-normal hf.xls (left); alks3831-5-10-a105 moderate hi ka fu x2.xls (right). The solid line represents the mean data for the simulated population and the dashed lines are the 5th and 95th percentiles of the population. Observed data: ALK3831-A105

**Reviewer's comments:**

- The Reviewer used the same SAM HI PBPK model to simulate the effect of HI on PK of SAM following a single (b) (4) dose of SAM 1 mg, as described in the Study (b) (4). The model was able to predict the observed clinical PK data in subjects with mild-to-severe HI following (b) (4) administration of SAM. As shown in **Table 14**, the predicted geometric mean C<sub>max</sub> and AUC ratios were within 25% of the observed data. Additionally, linear PK relationships of SAM were simulated, using the Applicant's SAM HI PBPK model, with dose levels of SAM ranging from 1-20 mg for both (b) (4) oral administration routes (results not shown). The Reviewer concluded the SAM HI PBPK model can be used to bridge the PK findings from SAM (b) (4) to SAM orally administered in HI population.
- The SAM HI PBPK model was then used to simulate the PK profiles following multiple oral doses of SAM 10 mg in HI subjects. PBPK predictions are presented in **Table 14**. For the severe HI population, PBPK analysis predicted a 2.1- and 2.6-fold increase in

C<sub>max</sub> and AUC of SAM, respectively, following multiple oral doses of SAM 10 mg for 14 days

The Applicant also conducted PBPK simulations which employed the predicted fup values for mild, moderate and severe HI subjects (fup =0.71, 0.76 and 0.81, respectively). The simulated results showed that increased fup in HI subjects had a small (<10%) impact on the magnitude of changes in SAM PK (Table 14).

**Table 14 Predicted and observed C<sub>max</sub> and AUC for SAM PK in HI subjects following single-dose and at steady-state**

	Health		Mild		Moderate		Severe	
	A single <sup>(b) (4)</sup> dose of 1 mg samidorphan; observed data <sup>(b) (4)</sup>							
	C <sub>max</sub> (ng/mL)	AUC inf (ng/mL.h)	C <sub>max</sub> R	AUC R	C <sub>max</sub> R	AUC R	C <sub>max</sub> R	AUC R
<b>Predicted (GM)#</b>	3.02	25.91	1.08	1.29	1.23	1.94	1.34	2.58
<b>Observed (GM)</b>	1.95	17.7	1.14	1.26	1.50	1.88	1.47	2.15
<b>P/O</b>			<b>0.94</b>	<b>1.02</b>	<b>0.82</b>	<b>1.03</b>	<b>0.92</b>	<b>1.20</b>
<b>A single oral dose of 10 mg samidorphan, observed data from ALK3831-A105</b>								
<b>Predicted (GM)*</b>	33.5	277	1.46	1.26	1.63	2.02	1.83	2.55
<b>Observed (GM)</b>	29.6	278			1.66	1.56		
<b>P/O</b>					<b>0.98</b>	<b>1.25</b>		
<b>Multiple oral doses of 10 mg samidorphan</b>								
<b>Predicted (GM)* (fup= 0.69)</b>	35.2	261	1.47	1.26	1.79	2.02	2.10	2.55
<b>Predicted (GM)*<sup>1</sup> (alternative fup)</b>	35.2	261	1.47	1.23	1.79	1.90	2.10	2.32

# Reviewer's independent analysis. \*Extracted from Tables 21, 23, and 24 (PBPK report #10);  
<sup>1</sup>SAM fup of 0.71, 0.76, and 0.81 for mild, moderate, and severe HI, respectively, were used in the simulations (see Table 9 summary) .

**Reviewer's comment:**

- There is limited experience on using PBPK modeling to evaluate the effect of HI in regulatory submission. The Reviewer found PBPK analysis couple with default HI virtual population might overestimate the effect of HI on a drug's PK<sup>2,3</sup>. One potential uncertainty is the impact of hepatic impairment on CYP expression and transporter activities<sup>4</sup>. In the current HI PBPK analysis, there was a good agreement between the

<sup>2</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf)

<sup>3</sup> Hall 2019. "PBPK 360- The State of Science. Industry Perspective" – Presentation at 2019 FDA PBPK Public Workshop. (<https://www.fda.gov/media/134098/download>)

<sup>4</sup> Jones et al., Clin Pharmacol Ther 2015 Mar;97(3):247-62

observed and predicted effect of HI (mild-to severe) on the PK of SAM. This fact gave the Reviewer confidence for supporting the application of HI PBPK analysis in this case.

- The Reviewer note that one rationale for the good predictive performance of the SAM HI PBPK analysis may rely on the drug's ADME characteristics. Given that SAM has a moderate fmCYP3A (= 0.33), the predicted HI effects might be less depended on the changes in enzyme abundance values in HI population. To evaluate the effects of reduce CYP enzyme abundance on the PK of SAM, the Reviewer conducted additional simulations by converting the CYP3A-mediated clearance to intrinsic hepatic clearance. In this case, the changes in the hepatic clearance was not impacted by the CYP enzyme abundance in HI subjects, but mainly driven by the reduced liver size. The predicted AUC ratios were 1.65 and 1.89 for subjects with moderate and severe HI, respectively, compared to HV. These predicted ratios were 20% lower than those predicted accounting for the reduced enzyme abundance values (results in **Table 14**). This exploratory analysis demonstrated that uncertainty in the magnitude of reduction in enzyme abundance in the HI population would have a minor impact on the predicted HI effect for SAM, given the fmCYP3A value is 0.33. Nevertheless, given the complex physiological effects of hepatic impairment, the discrepancy between prediction and observed PK changes in subjects with HI may be contributed from multiple factors rather than one specific parameter. Thus, more experience is needed to strength the applicability of PBPK modeling to prospectively estimate the effect of HI on a drug's PK.

#### 4.3.5 Conclusions

In summary, the Applicant's SAM PBPK model is adequate to predict the SAM PK following single- and multiple-dose administration and different administration routes.

PBPK analyses are adequate to predict the effect of itraconazole on SAM PK following sublingual and oral administration. The model predicted that itraconazole increased the SAM C<sub>max</sub> and AUC by 1.25- and 1.56-fold, respectively, when ALKS-3831 was given concomitantly.

Applicant's PBPK model is adequate to estimate the steady-state SAM exposures in subjects with mild, moderate, and severe hepatic impairment. The Applicant's final model predicted steady state AUC ratios of 1.3, 2.0 and 2.6 for SAM following multiple doses of ALKS-3831 in patients with mild, moderate, and severe hepatic impairment relative to subjects with normal hepatic function, respectively.

The review team proposed to include the following language in the USPI Section 12.3:

*Effect of other drugs on LYBALVI:* "Based on PBPK simulations, itraconazole, a strong CYP3A inhibitor, is predicted to increase samidorphan C<sub>max</sub> by 25% and AUC by 56%."

*Patients with Hepatic and Renal Impairment:* “Based on PBPK simulations, the predicted C<sub>max</sub> and AUC ratios for samidorphan in subjects with severe hepatic impairment relative to healthy subjects were 2.1- and 2<sup>(b)</sup><sub>(4)</sub> respectively.”

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 213378  
Supporting document/s: 1  
Applicant's letter date: 11/15/19  
CDER stamp date: 11/15/19  
Product: Lybalvi (Olanzapine and Samidorphan; ALKS 3831)  
Indication: Schizophrenia and Bipolar I Disorder  
Applicant: Alkermes Inc.  
Review Division: Psychiatry  
Reviewer: Amy M. Avila, PhD  
Supervisor/Team Leader: Aisar Atrakchi, PhD  
Division Director: Tiffany Farchione, MD (acting)  
Project Manager: Jasmeet (Mona) Kalsi, PharmD

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 213378 are owned by Alkermes Inc. or are data for which Alkermes Inc. has obtained a written right of reference.

Any information or data necessary for approval of NDA 213378 that Alkermes Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 213378.

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# 1 Executive Summary

## 1.1 Introduction

This application is a 505(b)(2) NDA for the fixed-dose combination drug product of olanzapine and samidorphan (Lybalvi), also known as ALKS 3831. The proposed indications are the treatment of schizophrenia and bipolar I disorder. Samidorphan is a new molecular entity (NME) and is not approved outside the U.S. Olanzapine is an FDA approved drug product; approved as Zyprexa in 1996 under NDA 020592. The current NDA relies in part on the Agency's previous findings of safety and efficacy of olanzapine, with Zyprexa as the listed drug. The fixed-dose combination product is being developed as a tablet for oral administration. This drug combination is not approved outside the U.S.

## 1.2 Brief Discussion of Nonclinical Findings

The nonclinical studies conducted with samidorphan (SAM) alone, and the combination of olanzapine (OLZ) and samidorphan (OLZ/SAM) submitted with the NDA, in addition to the Agency's previous findings of safety of OLZ, are adequate to assess the safety of the fixed-dose combination of OLZ/SAM for the treatment of schizophrenia and bipolar I disorder at a maximum recommended human dose of 20 mg/10 mg OLZ/SAM. A complete and adequate nonclinical program of studies was conducted for the NME, SAM. Nonclinical studies conducted with the combination of OLZ/SAM included pharmacology, pharmacokinetics, a 13-week repeat-dose toxicity study in dogs, and an embryofetal development study in rats. The Applicant's rationale for the combination drug product is that SAM presumably will mitigate OLZ-induced weight gain while maintaining the antipsychotic efficacy of OLZ.

SAM is an antagonist at mu-opioid receptors and a partial agonist at kappa-opioid receptors, with  $K_i$  values of 0.052 nM and 0.23 nM, respectively. OLZ is an atypical antipsychotic with activity at serotonin, dopamine, histamine 1, and alpha-adrenergic receptors. In vivo studies in rats co-administered OLZ and SAM demonstrated that SAM attenuates OLZ-induced increases in extracellular dopamine (DA) in response to a high fat diet. More importantly, SAM did not alter the activity of OLZ in a screen for antipsychotic efficacy in rats. SAM was also able to mitigate OLZ-induced metabolic dysfunction, including weight gain and adiposity, in rats and nonhuman primates (NHP), however it did not prevent OLZ-induced liver insulin resistance in rats or have any effects on HbA1c levels or glucose tolerance.

The overall pharmacokinetic profile of SAM in dogs is more closely related to humans than rats, including lack of sex difference in metabolism. Two metabolites formed in human plasma are present at levels greater than 10% of total radioactivity and are therefore considered major metabolites, RDC-9986 (N-dealkylated metabolite) and RDC-1066 (N-oxide). Both metabolites are formed in rats, dogs, and rabbits and have been adequately qualified in nonclinical studies assessing general toxicity, embryofetal development, and carcinogenicity. Interestingly, the more prominent metabolite formed in human plasma, RDC-9986, is pharmacologically active as it binds with high affinity to

mu-opioid receptors and functions in vitro as a mu-opioid receptor agonist which is in contrast to SAM which functions as an antagonist. In vivo rodent behavioral assays demonstrated that RDC-9986 functions as a partial opioid agonist. The overall pharmacodynamic effect of the combination of OLZ, SAM, and all major metabolites at clinically relevant concentrations is unclear. Co-administration of OLZ and SAM orally to dogs for 13-weeks or to pregnant rats did not significantly impact exposure or toxicokinetic parameters of either SAM or OLZ.

In safety pharmacology studies, SAM and metabolite RDC-9986 were not significant hERG channel blockers, and SAM did not have any significant adverse effects on cardiovascular or respiratory parameters in dogs at doses which are 20 times the maximum recommended human dose (MRHD) of 10 mg SAM based on AUC. SAM exposure to rats had no effects on CNS or neurobehavioral parameters except at the highest dose; the no effect level (NOEL) dose was greater than 3 times the MRHD based on AUC.

Toxicity of orally administered SAM was evaluated in rats and dogs up to 6-months and 9-months in duration, respectively. In rats, the main toxicities observed included a significant decrease in body weight which was more pronounced in males than females, and liver histopathology findings (hepatocellular cytoplasmic vacuolation) in high dose males which was partially reversible. These effects did not correlate with exposure to parent drug as males had lower exposure levels to the parent drug than females at equivalent doses. The no observed adverse effect level (NOAEL) for SAM in rats is 5 mg/kg/day, which is 0.4 and 5 times the MRHD in males and females, respectively based on AUC. In dogs, toxicities included a significant decrease in body weight in both sexes and transient CNS-related clinical signs (e.g., head shaking, and excessive salivation) that were reversible after drug cessation. The NOAEL for SAM in dogs is 1 mg/kg/day, which is approximately equal to the clinical exposure at the MRHD of 10 mg SAM based on AUC.

The effects of the combination of OLZ and SAM was investigated in a 13-week repeat-dose oral toxicity study in dogs with a 4-week recovery period. No new toxicities were identified with the co-administration of OLZ and SAM compared to toxicities identified with OLZ or SAM alone. CNS-related clinical signs including tremors and ataxia, and GI-related signs were observed in males and females after treatment with OLZ, SAM, and the combination. Reversible organ weight changes with accompanying microscopic findings were observed in male and female reproductive tract organs which were attributed to OLZ. Non-adverse, partially reversible, decreases in thymus weights with corresponding microscopic findings were observed in males only with OLZ, SAM, and the combination.

SAM was negative in a complete and adequate battery of genetic toxicology assays. SAM is also non-carcinogenic as it did not induce tumors in male and female rats administered SAM for up to 95 weeks at exposures which are approximately 32 and 237 times the MRHD based on AUC, respectively and did not induce tumors in rasH2 transgenic mice administered SAM for 6-months.

SAM administration to pregnant rats during the period of organogenesis resulted in decreased fetal weights, increased skeletal variations, and a slight increase in total malformations at doses that were maternally toxic and greater than 248 times the MRHD based on AUC. The NOAEL dose is approximately 29 times the MRHD based on AUC. SAM administration to pregnant rabbits during the period of organogenesis resulted in maternal toxicity, but no effects on embryofetal development at doses up to approximately 143 times MRHD based on AUC. The administration of the combination of SAM and OLZ to pregnant rats during the period of organogenesis resulted in similar effects on embryofetal development as the study with SAM administration alone, including skeletal variations, visceral variations, and skeletal malformations, at doses that were maternally toxic and greater than 6 and 448 times the MRHD of 20 mg/10 mg OLZ/SAM, respectively. SAM did not produce any adverse effects on male or female fertility in rats. SAM administration to rats during pregnancy and lactation resulted in reduced pup survival, lower birth weights, and decreased pup body weight gain at doses 188 times the MRHD based on AUC. The NOAEL dose is approximately 36 times the MRHD based on AUC.

The safety of the major human metabolites, RDC-9986 and RDC-1066, was adequately assessed in nonclinical species for chronic general toxicity, reproductive toxicity, and carcinogenicity. A drug substance impurity with a specification limit above the qualification threshold (>NMT (b)(4)%) has been adequately qualified in nonclinical studies. Nonclinical data describing the primary pharmacodynamics, metabolism, genotoxicity, carcinogenicity, and developmental and reproductive toxicity of OLZ will be taken from the approved label of Zyprexa, the listed drug for this 505(b)(2) NDA.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

Based on the review and evaluation of the nonclinical data and supporting information for samidorphan and olanzapine, this application is recommended for approval from a Pharmacology/Toxicology perspective for the indication of schizophrenia and bipolar I disorder.

#### **1.3.2 Additional Nonclinical Recommendations**

None

#### **1.3.3 Labeling**

At the time this review was finalized, labeling negotiations with the Applicant were ongoing.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 1204592-75-5

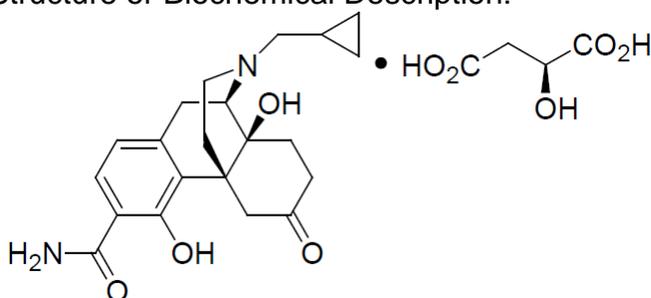
Generic Name: Samidorphan L-malate

Code Name: RDC-0313-02; ALKS 33

Chemical Name: Morphinan-3-carboxamide, 17-(cyclopropylmethyl)-4, 14-dihydroxy-6-oxo-, (2S)-2-hydroxybutanedioate

Molecular Formula/Molecular Weight:  $C_{21}H_{26}N_2O_4 \cdot C_4H_6O_5$  / 504.53 g/mol

Structure or Biochemical Description:



Pharmacologic Class: opioid antagonist

CAS Registry Number: 132539-06-1

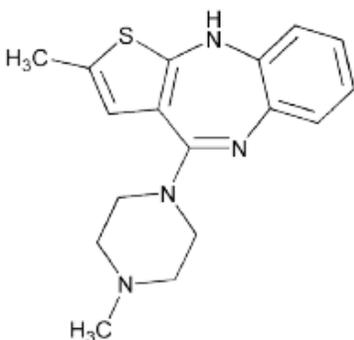
Generic Name: olanzapine

Code Name: OLZ

Chemical Name: 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine

Molecular Formula/Molecular Weight:  $C_{17}H_{20}N_4S$  / 312.44 g/mol

Structure or Biochemical Description:



Pharmacologic Class: atypical antipsychotic

### 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 114375: ALKS 3831 (samidorphan and olanzapine) for schizophrenia

NDA 020592: Zyprexa (olanzapine) tablets approved 1996

### 2.3 Drug Formulation

Tablets: ALKS 3831 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, 20 mg/10 mg (olanzapine/samidorphan)

**Table 1: Composition of ALKS 3831 Tablets To-Be-Marketed Formulation**

Function Component	Tablet Strength (OLZ/SAM)			
	5 mg/10 mg	10 mg/10 mg	15 mg/10 mg	20 mg/10 mg
	Amount per Coated Tablet, mg (% wt/wt)			
<b>Drug Substance</b>				
OLZ	5.00 (b) (4)	10.00 (b) (4)	15.00 (b) (4)	20.00 (b) (4)
SAM L-malate	13.62	13.62	13.62	13.62 (b) (4)

Abbreviations: NF=National Formulary; OLZ=olanzapine; SAM=samidorphan.

[Source: NDA 213378: Clinical Overview]

### 2.4 Comments on Novel Excipients

NA

### 2.5 Comments on Impurities/Degradants of Concern

The impurities in the samidorphan L-malate drug substance are either unknown impurities that are controlled at  $\leq$  (b) (4) % or known impurities that are controlled at  $\leq$  (b) (4) % each in accordance with ICH Q3A(R2), except for one impurity, (b) (4) in which the Applicant has set an individual specification limit of (b) (4) % w/t. The Applicant justified the limit based on qualification in toxicology studies and that the impurity lacked

structural alerts when screened using adequate *in silico* QSAR methodologies. In addition, the CDER Computational Toxicology group conducted a QSAR assessment on impurity (b) (4) and confirmed it to be negative for bacterial mutagenicity. Impurity (b) (4) was present at a level of (b) (4) % in (b) (4) that was used in both the GLP Ames assay and GLP *in vitro* chromosomal aberration test. Impurity (b) (4) was present at a level of (b) (4) % (b) (4) used in the GLP *in vivo* mouse micronucleus test; noted the impurity was not tested neat in these studies. Each of those genotoxicity tests were negative. (b) (4) is considered a non-genotoxic impurity. (b) (4) was present at a level of (b) (4) % (b) (4) that was used in the 26-week and 39-week chronic repeat-dose rat and dog toxicity studies, respectively. The amount of impurity (b) (4) used in the GLP rat embryofetal development study (batch no. 1425-83-1) was (b) (4) %. The amount of impurity (b) (4) exposed to dogs at the high dose of 10 mg/kg/day in 39-week study, was (b) (4) mg/kg/day ((b) (4) x 10 mg/kg/day). The human equivalent dose (HED) is (b) (4) mg/kg/day (b) (4) mg/kg/day x (b) (4) conversion factor). Based on a 60 kg adult, this equates to a safe dose of (b) (4) mg/day for impurity (b) (4). The maximum amount of impurity (b) (4) at the top clinical dose of samidorphan (10 mg), based on a specification limit of (b) (4) %, is (b) (4) µg/day. The specification limit of NMT (b) (4) 3% for impurity (b) (4) is acceptable from a nonclinical standpoint. There are no degradants in the drug product that require nonclinical qualification.

The Applicant conducted an assessment of all known impurities, degradation products and potential impurities in the manufacturing process of samidorphan L-malate according to ICH M7 (study 702-06951). An expert rule-based (Derek Nexus versions 4.1.0 and 6.0.1) and a statistical-based (Sarah Nexus versions 1.2.0 and 3.0.0) *in silico* prediction tools were used. One potential impurity, (b) (4) was identified as equivocal in the Derek Nexus *in silico* prediction for mutagenicity. A GLP Ames assay was conducted with (b) (4) and the assay was negative; therefore, the potential impurity will be controlled as a non-genotoxic impurity. Any known potential mutagenic impurities in the manufacturing process are being controlled to NMT (b) (4) ppm, which would be less than (b) (4) µg/day based on the MRHD of 10 mg samidorphan in the ALKS 3831 drug product.

## 2.6 Proposed Clinical Population and Dosing Regimen

Proposed ALKS 3831 dose range of 5/10 mg, 10/10 mg, 15/10 mg, and 20/10 mg, with once-daily dosing given with or without food for the treatment of adults with schizophrenia or bipolar I disorder.

## 2.7 Regulatory Background

A pre-NDA meeting was held on May 7, 2019.

### 3 Studies Submitted

#### 3.1 Studies Reviewed

**Table 2: List of nonclinical studies conducted and submitted with samidorphan alone and the olanzapine/samidorphan combination**

Study/Study No.	Concentration or Dose	Compliance Status	Tabulated Summary
<b>Safety Pharmacology/Toxicokinetic Studies with Samidorphan Alone<sup>a</sup></b>			
hERG (AT-0313-09)	3, 10, 30, 60 µM	GLP	2.6.3.4 AT-0313-09
Isolated Perfused Rabbit Heart (AT-0313-15)	0.5, 5, 50 µM	Non-GLP	2.6.3.4 AT-0313-15
Cardiovascular/ Respiratory Assessment in Dogs (AT-0313-10)	0.5, 3, 10 mg/kg	GLP	2.6.3.4 AT-0313-10
Neurofunctional Assessment in Rats (AT-0313-11)	3.5, 35, 350 mg/kg	GLP	2.6.3.4 AT-0313-11
<b>Single-Dose Toxicity/Toxicokinetic Studies with Samidorphan Alone</b>			
Single-dose Oral Study in Rats (AT-0313-03)	35, 110, 350 mg/kg	GLP	2.6.7.5 AT-0313-03
Single-dose Oral and IV Study in Dogs (AT-0313-01)	1 mg/kg IV 1, 3, 10, 20, 40 mg/kg oral	Non-GLP	2.6.7.5 AT-0313-01
<b>Repeat-Dose Toxicity/Toxicokinetic Studies with Samidorphan Alone</b>			
4-Week Range-finding Oral Study in Mice (AT-0313-27)	30, 100, 300, 600 mg/kg/day	GLP	2.6.7.7 AT-0313-27
4-Week Range-finding Oral Study in Mice (AT-0313-28)	300, 450, 600 mg/kg/day for 28 days; 750 mg/kg/day for 14 days	GLP	2.6.7.7 AT-0313-28
2-Week Oral Study in Rats with 2-Week Recovery Period (AT-0313-07)	35, 110, 350 mg/kg/day	GLP	2.6.7.7 AT-0313-07
13-Week Oral Study in Rats with 4-Week Recovery Period (AT-0313-18)	25, 75, 250 mg/kg/day	GLP	2.6.7.7 AT-0313-18
26-Week Oral Study in Rats with 4-Week Recovery Period (AT-0313-16)	0.5, 5, 50 mg/kg/day	GLP	2.6.7.7 AT-0313-16

Study/Study No.	Concentration or Dose	Compliance Status	Tabulated Summary
<b>Repeat-Dose Toxicity/Toxicokinetic Studies with Samidorphan Alone (continued)</b>			
5-Day Oral Dose Range-finding Study in Dogs (AT-0313-02)	20 mg/kg/day	Non-GLP	2.6.7.6 AT-0313-02
2-Week Oral Study in Dogs with 2-Week Recovery Period (AT-0313-08)	1, 3, 10 mg/kg/day	GLP	2.6.7.7 AT-0313-08
13-Week Oral Study in Dogs with 4-Week Recovery Period (AT-0313-17)	1, 3, 10 mg/kg/day	GLP	2.6.7.7 AT-0313-17
39-Week Oral Study in Dogs with 4-Week Recovery Period (AT-0313-19)	1, 3, 10 mg/kg/day	GLP	2.6.7.7 AT-0313-19
<b>Genotoxicity Studies with Samidorphan Alone</b>			
<i>In vitro</i> Bacterial Mutagenicity (AT-0313-04)	1.5-5000 µg/plate (preliminary) 50-5000 µg/plate (confirmatory)	GLP	2.6.7.8 AT-0313-04
<i>In vitro</i> Mammalian Chromosome Aberration (AT-0313-05)	0.5-5000 µg/mL (preliminary) 25-750 µg/mL (confirmatory)	GLP	2.6.7.8 AT-0313-05
<i>In vivo</i> Oral Micronucleus Study in Mice (AT-0313-06)	35, 110, 350, 650, 875 or 1100 mg/kg (preliminary) 42, 120 and 420 mg/kg (definitive)	GLP	2.6.7.9 AT-0313-06
<b>Carcinogenicity/Toxicokinetic Studies with Samidorphan Alone<sup>b</sup></b>			
26-week Oral Carcinogenicity Study in <i>rasH2</i> Mice (AT-0313-37)	125, 250 500 mg/kg/day	GLP	2.6.7.10 AT-0313-37
2-Year Oral Carcinogenicity Study in Rats (AT-0313-26)	Males: 20, 35, 75 mg/kg/day; Females: 15, 30, 60 mg/kg/day	GLP	2.6.7.10 AT-0313-26

Study/Study No.	Concentration or Dose	Compliance Status	Tabulated Summary
<b>Developmental and Reproductive Toxicity/Toxicokinetic Studies with Samidorphan Alone</b>			
Oral Fertility and Early Embryonic Development Study in Male Rats (AT-0313-24)	10, 30, 100 mg/kg/day	GLP	2.6.7.12 AT-0313-24
Oral Fertility and Early Embryonic Development Study in Female Rats (AT-0313-25)	30, 150, 450 mg/kg/day	GLP	2.6.7.12 AT-0313-25
Oral Dose Range-finding Embryofetal Development Study in Rats (AT-0313-20)	50, 150, 450, 1000 mg/kg/day	Non-GLP	2.6.7.11 AT-0313-20
Oral Embryofetal Development Study in Rats (AT-0313-22)	25, 100, 300 mg/kg/day	GLP	2.6.7.13 AT-0313-22
Oral Dose Range-finding Embryofetal Development Study in Rabbits (AT-0313-21)	2, 10, 20, 200 mg/kg/day in non-pregnant phase; 3, 10, 30, 100 mg/kg/day in pregnant phase	Non-GLP	2.6.7.11 AT-0313-21
Oral Embryofetal Development Study in Rabbits (AT-0313-23)	10, 30, 90 mg/kg/day	GLP	2.6.7.13 AT-0313-23
Oral Pre-postnatal Development Study in Rats (AT-0313-38)	10, 30, 100 mg/kg/day	GLP	2.6.7.14 AT-0313-38
<b>Repeat-Dose Toxicity/Toxicokinetic Studies with ALKS 3831 (OLZ and SAM Combination)</b>			
21-Day Oral Study in Dogs (AT-0313-33)	OLZ/SAM (mg/kg/day): 10/0, 5/10, 10/10	Non-GLP	2.6.7.6 AT-0313-33
13-Week Oral Study in Dogs with 4-Week Recovery Period (AT-0313-34)	OLZ/SAM (mg/kg/day): 5/0, 0/10, 1.5/3, 5/10	GLP	2.6.7.7 AT-0313-34

Study/Study No.	Concentration or Dose	Compliance Status	Tabulated Summary
<b>Developmental and Reproductive Toxicity/Toxicokinetic Studies with ALKS 3831 (OLZ and SAM Combination)</b>			
Oral Dose Range-finding Embryofetal Development Study in Rats (AT-0313-44)	OLZ/SAM (mg/kg/day): 8/0, 0/300, 0.5/10, 2/30, 4/100, 8/300	Non-GLP	2.6.7.11 AT-0313-44
Oral Embryofetal Development Study in Rats (AT-0313-45)	OLZ/SAM (mg/kg/day): 0.5/10, 2/50, 6/200, 0/200	GLP	2.6.7.13 AT-0313-45

Abbreviations: GLP=Good Laboratory Practice; IV=intravenous; OLZ = olanzapine; SAM=samidorphan

<sup>a</sup> RDC-9986, a major human metabolite of samidorphan, also was evaluated in the hERG assay (AT-9986-01).

<sup>b</sup> Carcinogenicity study designs were reviewed by FDA's Executive Carcinogenicity Assessment Committee prior to initiation.

[Source: Nonclinical Overview section of NDA 213378.]

### 3.2 Studies Not Reviewed

Written reviews of analytical methods study reports were not conducted.

### 3.3 Previous Reviews Referenced

The Applicant has developed ALKS 3831 under the 505(b)(2) pathway using Zyprexa tablets as the listed drug. The Applicant is relying in part on the Agency's previous findings of safety for olanzapine, as described in the package insert for Zyprexa. Below is the Applicant's table listing the nonclinical information being used from the label of Zyprexa to support the approval of ALKS 3831.

**Table 3: Nonclinical References for Approved Findings for the Listed Drug Olanzapine (Zyprexa®)**

Study Type	Reference
Introduction (Section 2.6.1)	Zyprexa Package Insert (Zyprexa USPI)
Primary Pharmacodynamics (Section 2.6.2.2.1)	
Metabolism (Sections 2.6.4.1.1)	
Genotoxicity (Section 2.6.6.4.1)	
Carcinogenicity (Section 2.6.6.5.1)	
Developmental and Reproductive Toxicology (DART) (Section 2.6.6.6.1)	
Primary Pharmacodynamics (Section 2.6.2.2.1)	
Abuse Potential (Section 2.6.2.4.4.1)	
Absorption, Distribution, Metabolism and Excretion (Section 2.6.4.1.1)	
Safety Pharmacology (Section 2.6.2.4.1)	Zyprexa® (NDA 020592)
Toxicology (Sections 2.6.6.2.1, 2.6.6.3.1, and 2.6.6.7)	Zyprexa® Package Insert (Zyprexa USPI); Zyprexa® (NDA 020592)

[Source: NDA 213378, Nonclinical Overview]

## 4 Pharmacology

### 4.1 Primary Pharmacology

#### Olanzapine (OLZ):

The Applicant did not conduct any pharmacology studies with OLZ alone; however, the following information on the mechanism of action and pharmacodynamics of OLZ is included in the label for the listed drug, Zyprexa.

*The mechanism of action of olanzapine, in the listed indications is unclear. However, the efficacy of olanzapine in schizophrenia could be mediated through a combination of dopamine and serotonin type 2 (5HT<sub>2</sub>) antagonism.*

*Olanzapine binds with high affinity to the following receptors: serotonin 5HT<sub>2A/2C</sub>, 5HT<sub>6</sub> (K<sub>i</sub>=4, 11, and 5 nM, respectively), dopamine D<sub>1-4</sub> (K<sub>i</sub>=11-31 nM), histamine H<sub>1</sub> (K<sub>i</sub>=7 nM), and adrenergic α<sub>1</sub> receptors (K<sub>i</sub>=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT<sub>3</sub> (K<sub>i</sub>=57 nM) and muscarinic M<sub>1-5</sub> (K<sub>i</sub>=73, 96,*

132, 32, and 48 nM, respectively). Olanzapine binds with low affinity to GABA<sub>A</sub>, BZD, and  $\beta$ -adrenergic receptors ( $K_i > 10 \mu\text{M}$ ).

#### Samidorphan (SAM):

##### In vitro studies:

In in vitro receptor binding assays, SAM displayed nanomolar affinity for human  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors,  $K_i$  values of 0.052, 0.23, and 2.7 nM, respectively. However, in vitro functional activity assays demonstrated that SAM acts as an antagonist at  $\mu$ -opioid receptors ( $\text{IC}_{50}$  of 0.88 nM and  $I_{\text{max}}$  of 92%) with no agonist activity, and acts as a partial, low activity, agonist at both  $\kappa$ -, and  $\delta$ -opioid receptors with  $\text{EC}_{50}$  values of 3.2 nM, and 1.8 nM and maximal stimulation ( $E_{\text{max}}$ ) values of 36% and 35%, respectively.

**Table 4:  $K_i$  values for samidorphan and major metabolites, RDC-9986 and RDC-1066**

Compound	Human Opioid Receptor and Ligand		
	$K_i$ (nM)		
	$\mu$ [ <sup>3</sup> H] DAMGO	$\kappa$ [ <sup>3</sup> H] U69,593	$\delta$ [ <sup>3</sup> H] Naltrindole
Samidorphan	0.052	0.23	2.7
RDC-9986	0.26	23	56
RDC-1066	8.1	110	280

Source: 702-03231 [samidorphan]; 702-03234 [RDC-9986]; 702-07219 [RDC-1066].

[Source: NDA 213378, Pharmacology written summary]

**Table 5: In vitro functional activity of samidorphan and major metabolites RDC-9986 and RDC-1066**

Compound	$\mu$ -Opioid Receptor				$\kappa$ -Opioid Receptor				$\delta$ -Opioid Receptor			
	Agonist Mode		Antagonist Mode		Agonist Mode		Antagonist Mode		Agonist Mode		Antagonist Mode	
	$\text{EC}_{50}$ (nM)	$E_{\text{max}}$ (%)	$\text{IC}_{50}$ (nM)	$I_{\text{max}}$ (%)	$\text{EC}_{50}$ (nM)	$E_{\text{max}}$ (%)	$\text{IC}_{50}$ (nM)	$I_{\text{max}}$ (%)	$\text{EC}_{50}$ (nM)	$E_{\text{max}}$ (%)	$\text{IC}_{50}$ (nM)	$I_{\text{max}}$ (%)
Samidorphan	NA	3.8 $\pm$ 0.67	0.88 $\pm$ 0.14	92 $\pm$ 2.9	3.2 $\pm$ 1.2	36 $\pm$ 0.98	38 $\pm$ 8.9	57 $\pm$ 0.71	1.8 $\pm$ 0.5	35 $\pm$ 4.2	6.9 $\pm$ 2.1	56 $\pm$ 3.1
RDC-9986	17	98	ND <sup>a</sup>	No Inhibition	53	90	ND <sup>a</sup>	No Inhibition	130	80	ND <sup>a</sup>	No Inhibition
RDC-1066	37 $\pm$ 5.1	13 $\pm$ 1.1	150 $\pm$ 7.5	88 $\pm$ 1.5	NT	NT	NT	NT	NT	NT	NT	NT

Abbreviations: ND<sup>a</sup>=not determined; NT=not tested

<sup>a</sup> >10  $\mu\text{M}$

Note: Values for RDC-9986 were determined once, and values for RDC-1066 were determined in triplicate.

Source: 702-03231 [Samidorphan]; 702-03234 [RDC-9986]; 702-07219 [RDC-1066].

[Source: NDA 213378, Pharmacology written summary]

##### In vivo studies:

In vivo studies were conducted in rodents to investigate the potential opioid receptor agonist and antagonist activity of SAM. SAM did not demonstrate any measurable antinociceptive activity (a measure of opioid receptor agonist activity) in two standard thermal pain models, the hot plate test in mice and rats and the tail flick test in rats

(studies 702-03368 and 702-03438), and in an inflammatory pain model in rodents, the inflammatory writhing pain (abdominal stretching) assay (study 702-03437). Unlike other assays, the writhing assay also responds to compounds that have low intrinsic opioid activity or act as partial agonists. SAM was shown to act as an opioid antagonist in vivo through its ability to block or reverse the effects of full mu-opioid agonists morphine or fentanyl. Specifically, pretreatment of rats with SAM (oral or subcutaneous) 30 minutes prior to administration of morphine, blocked the antinociceptive effects of morphine in the tail flick or hot plates assays (studies 702-03368 and 702-03371). In male beagle dogs, single intramuscular injections of SAM (0.1 mg/kg and 0.2 mg/kg) 1.5 hours after initiation of fentanyl infusions, generally reversed the fentanyl-induced sedation and respiratory depression, and fentanyl-induced decreases in body temperature and increases in heart rate (study 00081). The respiratory function assessment data in dogs was variable. SAM was also able to reverse some of the fentanyl-induced effects (sedation, respiratory depression, decreased body temperature) in cynomolgus monkeys that were administered a single intramuscular injection of SAM (0.4 mg/kg) 60 to 150 minutes following initiation of fentanyl infusion (study 01675).

#### Samidorphan metabolites:

There are two major circulating human metabolites of SAM observed in plasma at greater than 10% of total drug-related exposure based on radioactivity, RDC-9986 (N-dealkylated metabolite) and RDC-1066 (N-oxide of SAM), at 19% and 14% of total radioactivity ( $AUC_{0-8hr}$ ), respectively. Although metabolite RDC-9986 has lower affinity for human mu-, kappa-, and delta-opioid receptors than SAM, it still has significant, sub-nanomolar, affinity for the human mu-opioid receptor ( $K_i$  of 0.26 nM). Metabolite RDC-1066 has significantly less affinity for all three receptors (>100-fold lower binding) compared to SAM. In vitro functional assays demonstrated that RDC-9986 acts as an agonist at all three opioid receptors with  $EC_{50}$  values of 17 nM, 53 nM, and 130 nM, at the mu-, kappa-, and delta-opioid receptors, respectively. Functional activity for RDC-1066 was only tested for the mu-opioid receptor, and it was determined to function in vitro as an antagonist.

RDC-9986 was additionally tested in in vivo assays to assess its opioid agonist activity. RDC-9986 did not show any antinociceptive effects in the hot plate test in male Sprague-Dawley rats administered subcutaneous doses of RDC-9986 up to 20 mg/kg (study 702-07222). The positive control morphine did show significant antinociceptive effects. In another assay, complete Freund's adjuvant (CFA)-induced inflammatory pain model, RDC-9986 (0.15 and 1 mg/kg, SC to male rats) had a statistically significant and dose-dependent analgesic response. A positive control, such as morphine, was not used in this assay therefore the effects of RDC-9986 compared to a full, potent, opioid agonist are not known. The Applicant noted that the CFA-induced inflammatory pain model is sensitive to low intrinsic (partial) opioid agonist, unlike the hot plate test which may explain why no functional activity was detected for RDC-9986 in the hot plate tests. Additionally, it is noted that the pain model assays were all conducted in male rats only. The metabolism of parent drug, SAM, is very different in male and female rats with males having much lower exposure to SAM than females at equivalent doses. The metabolism of RDC-9986 in male versus female rats is unknown and plasma exposure levels to RDC-9986 were not measured in the above pain model assays. RDC-9986

displayed significant antinociceptive effects to thermal pain in a hot plate assay using Swiss-Webster (CFW) mice administered subcutaneous doses of RDC-9986 at 15 and 30 mg/kg (study 702-07223).

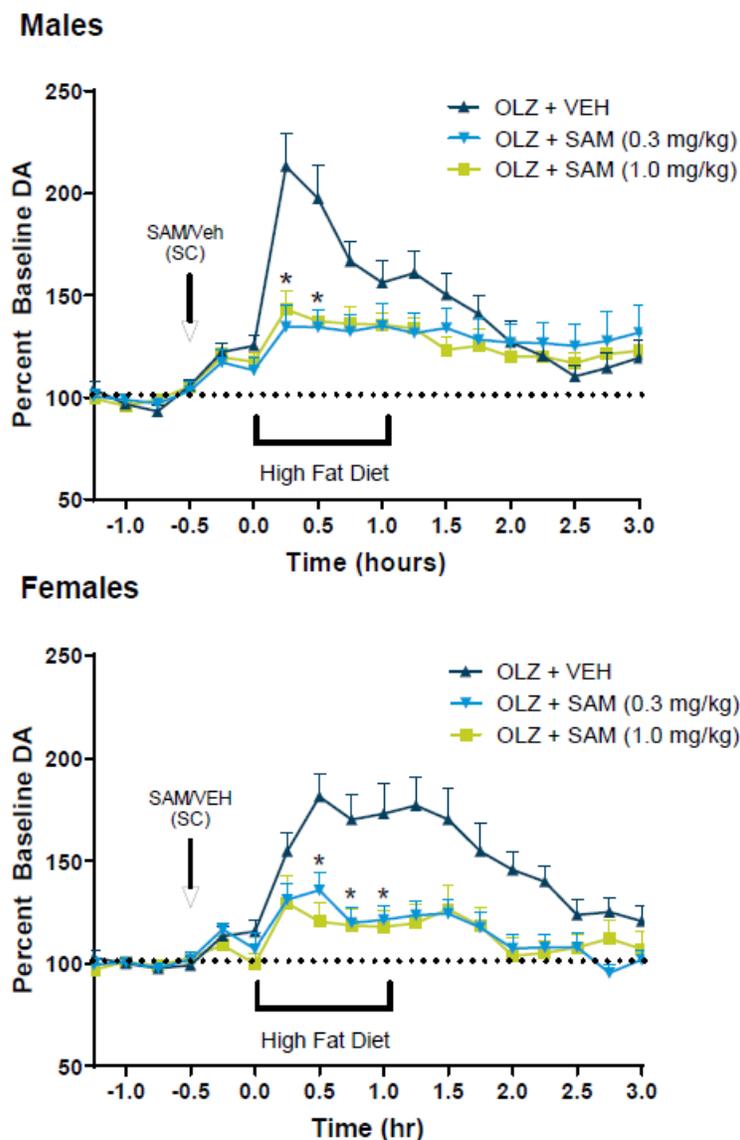
The elimination half-life ( $t_{1/2}$ ) of RDC-9986 in animals and humans is longer than that of SAM, therefore the pharmacodynamic effects of RDC-9986 may persist after cessation of SAM exposure. The overall contribution of RDC-9986 to the pharmacodynamic effect of the combination of OLZ and SAM at clinically relevant doses is unknown.

Olanzapine and samidorphan (ALKS 3831):

In vivo studies:

Administration of OLZ pamoate (long-acting injectable formulation) (100 mg/kg, SC) resulted in a significant increase in extracellular levels of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the nucleus accumbens shell of male and female Sprague-Dawley rats in response to a high fat diet, as measured via microdialysis 48 hours after administration (study 702-07869). Co-administration of SAM (0.3 mg/kg or 1 mg/kg, BID SC) attenuated the OLZ-induced increase in dopamine, DOPAC, and HVA in response to the high-fat diet.

**Figure 1 Samidorphan Attenuates Olanzapine-Induced Increase in Dopamine Response to High Fat Diet in Nucleus Accumbens in Rats**



Abbreviations: SC=subcutaneous; DA=dopamine; OLZ=olanzapine; SAM=samidorphan; VEH=vehicle;

ANOVA=analysis of variance; HSD=honestly significant difference

Data shown as mean + standard error of the mean (SEM)

\*  $P < 0.01$  OLZ/VEH vs OLZ/SAM (two-way ANOVA with repeated measures; Tukey HSD *post-hoc* analysis)

Source: 702-07869

[Source: NDA 213378, Pharmacology written summary]

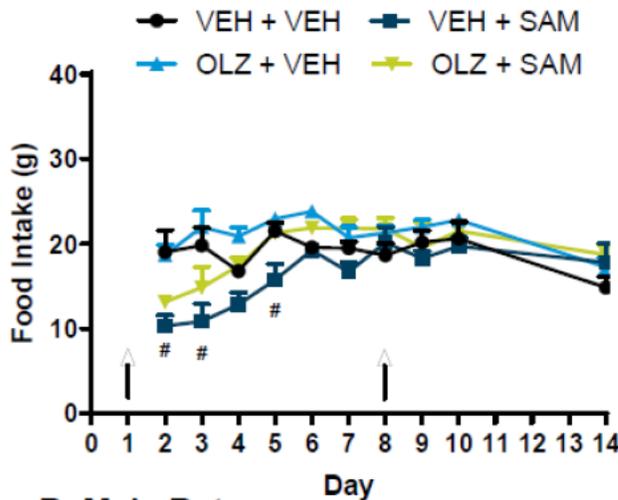
OLZ pamoate (100 mg/kg, SC) produced a decrease in locomotor activity in female Sprague-Dawley rats while SAM (0.96 mg/rat/day, SC via osmotic pump) produced an increase in locomotor activity, although the effects were not statistically significant compared to controls due to variability between animals (702-07990). Antagonism of amphetamine-induced hyperlocomotor activity in rodents is a common rodent behavioral model used to measure antipsychotic-like activity of drugs. Oral

administration of OLZ (0.3 to 3.0 mg/kg) to female Sprague-Dawley rats dose-dependently attenuated amphetamine (1.5 mg/kg)-induced hyperlocomotor activity and co-administration of SAM (2 mg/kg, SC) did not alter OLZ's effects (study 702-03187). In another study, co-administration of SAM (3.8 mg/kg/day, SC via osmotic pump) with OLZ pamoate (100 mg/kg, SC) to female Sprague-Dawley rats did not alter the ability of OLZ to decrease AMPH-induced hyperlocomotor (study 702-07733). Therefore, the route of administration, hence metabolite formation, had no effect of SAM's role on the OLZ response.

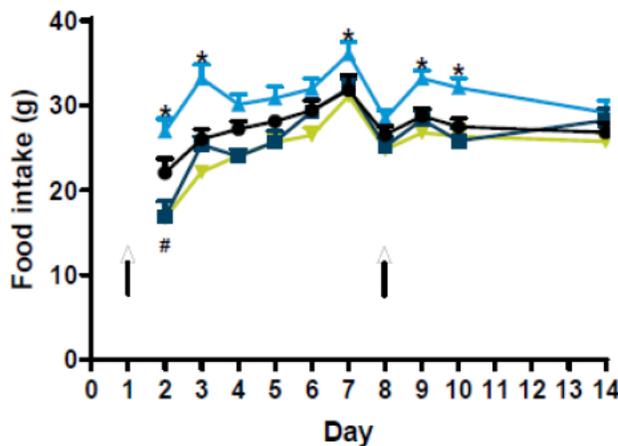
Administration of OLZ pamoate (100 mg/kg, SC) to female Sprague-Dawley rats for 28 days resulted in a significant increase in body weight compared to vehicle treated rats, and co-administration of SAM (16 mg/ml administered SC via implanted ALZET osmotic pump for 28 days) attenuated the increase in weight gain (study 702-07801). In contrast to female rats, OLZ treatment in male rats did not cause an increase in weight gain compared to vehicle control. In both sexes, SAM administration alone produced a significant decrease in body weight compared to vehicle control. OLZ significantly increased body fat composition in male and female rats compared to vehicle controls and SAM attenuated the adipose accumulation in rats treated with OLZ. In female rats, SAM treatment alone significantly decreased body fat composition compared to vehicle treated rats. OLZ treatment alone produced a transient significant increase in food consumption in male rats, while SAM treatment alone produced a transient significant decrease in food consumption in female rats. The differential effects of SAM treatment observed in food consumption and body weight in male and female rats may be due to sex differences in metabolism of SAM in rats.

**Figure 2 Effects of Olanzapine, Samidorphan or the Combination on Food Consumption**

**A. Female Rats**



**B. Male Rats**



Abbreviations: g=grams; OLZ=olanzapine; SAM=samidorphan; SEM=standard error of the mean; VEH=vehicle;

ANOVA=analysis of variance;

Arrows denote days of administration of the OLZ. Data shown as mean +SEM

\*  $P < 0.05$  OLZ/VEH vs VEH/VEH

#  $P < 0.01$  OLZ/VEH vs OLZ/SAM

Statistical analysis with two-way ANOVA with repeated measures and Dunnett's post-hoc test

Source: 702-07801

[Source: NDA 213378, Pharmacology written summary]

**Figure 3 Effects of Olanzapine, Samidorphan or the Combination on Weight Gain and Adiposity in Female and Male Sprague-Dawley Rats**

**Female Rats**

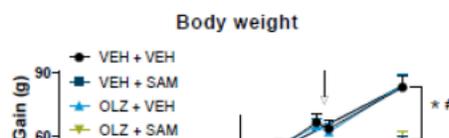
**Male Rats**

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**A.**



**C.**



A. \* $P < 0.001$  VEH/VEH vs OLZ/VEH; # $P < 0.05$  OLZ/VEH vs OLZ/SAM; & $P < 0.01$  VEH/VEH vs VEH/SAM  
B. \* $P < 0.001$  VEH/VEH vs OLZ/VEH; # $P < 0.001$  VEH/VEH vs VEH/SAM  
C. \* $P < 0.001$  VEH/VEH vs VEH/SAM; # $P < 0.01$  VEH/VEH vs OLZ/VEH  
D. \* $P < 0.01$  VEH/VEH vs OLZ/VEH; # $P < 0.05$  OLZ/VEH vs OLZ/SAM  
Statistical tests: Body Weight=one-way ANOVA and Tukey HSD post-hoc test; Fat Mass=two-way ANOVA and Tukey HSD post-hoc test  
Source: 702-07801

[Source: NDA 213378, Pharmacology written summary]

OLZ pamoate (100 mg/kg, SC) significantly decreased glucose clearance following a bolus insulin administration in female and male Sprague-Dawley rats, while co-administration of SAM (administered SC via osmotic pumps at doses of 125 mg/mL for males 40 mg/mL for females) restored and partially restored normal glucose clearance in female and male rats, respectively (study 702-07811). In a similarly designed study, SAM attenuated OLZ-induced decreases in glucose utilization when co-administered to female Sprague-Dawley rats; but did not prevent OLZ-induced liver insulin resistance. SAM partially prevented OLZ-induced muscle insulin resistance as well as glucose uptake increase in adipose tissue (study 702-08003).

A study in female cynomolgus monkeys measured the effects of daily oral OLZ treatment (titrated from 1 mg/kg to 6 mg/kg) and co-administration of SAM (0.4 mg/kg, intramuscular injection) on body weight, adipose secretion, and metabolic changes (study 702-08004). Treatment of monkeys for 28 days with OLZ resulted in increases in body weight, adipose tissue accretion, triglycerides and LDLs compared to vehicle treated animals. Co-administration of SAM diminished the rate of weight gain and adipose accretion and prevented OLZ-induced elevations in triglycerides and LDL concentrations. There were no drug-related effects on HbA1c levels or effects on glucose tolerance.

## 4.2 Secondary Pharmacology

The potential for SAM and metabolites RDC-9986 and RDC-1066, at concentrations of 10  $\mu$ M, to bind to off-target receptors was evaluated in three separate in vitro assays which measured inhibition of receptor, transporter, or enzyme binding in a panel of 104 assays (studies AT-0313-12, AT-9986-02, and AT-1066-01, respectively). SAM and metabolite RDC-1066 did not inhibit binding to any other receptors, transporters, or enzymes greater than 50% besides to the mu-, kappa-, and delta-opioid receptors. Besides inhibition of binding to the mu-, kappa-, and delta-opioid receptors, metabolite RDC-9986 minimally inhibited binding to the serotonin (5-HT) transporter (54.1% reduction in binding at 10  $\mu$ M).

### 4.3 Safety Pharmacology

Safety pharmacology studies were conducted with the NME drug, SAM, only, and not the ALKS 3831 (OLZ/SAM) combination drug product. This approach is consistent with ICH M3(R2) and was agreed upon by the Division. Exposure multiples were calculated relative to steady-state exposure data in humans at the maximum recommended human dose (MRHD) of 10 mg SAM following repeated daily oral administration of ALKS 3831 20/10 mg from clinical study ALK3831-A104;  $C_{max}$  and  $AUC_{0-24h}$  of 46.0 ng/mL and 364 ng\*hr/mL for SAM, 15.1 ng/mL and 186 ng\*hr/mL for RDC-9986, and 9.0 ng/mL and 61.1 ng\*hr/mL for RDC-1066 (based on total exposure).

#### CNS:

Neurofunctional effects of SAM were assessed in male Sprague-Dawley rats after single oral gavage administration at 0, 3.5, 35, or 350 mg/kg, in a GLP study using a functional observation battery (FOB) starting approximately 60 minutes after dosing. At the highest dose tested of 350 mg/kg, there was a statistically significant reduced response during hand-to-hand transfer, increased salivation, reduced crossing and rearing in an open-field test, and reduced rectal temperature compared to control. In addition, there were stereotypical behaviors such as rubbing of chins on cage surfaces and excessive burrowing in the high dose animals. The Applicant noted that similar behaviors have been described with other drugs that modulate opioid receptors. The NOEL for CNS/neurobehavioral activity in rats is 35 mg/kg. The NOEL dose provides nonclinical to clinical exposure multiples for SAM and its 2 metabolites, RDC-9986, and RDC-1066, greater than 15, 189, and 3 times for  $C_{max}$  and greater than 3, 51, and 0.6 times for AUC, respectively, compared to exposures in humans at the MRHD of 10 mg SAM. Rat exposure data were based on a 25 mg/kg/day dose from a 14-day bridging toxicokinetic study (AT-0313-41).

Several abuse potential nonclinical studies (self-administration, measurement of extracellular dopamine levels, physical dependence) either stand-alone or as part of general toxicity studies, were conducted for SAM. These studies, along with the human abuse potential, are reviewed by the Controlled Substance Staff (CSS). Refer to the CSS consult review.

#### Cardiovascular:

In a GLP hERG patch clamp assay, SAM inhibited the hERG potassium current by 9.2%, 28.4%, 52.0%, and 66.2% at 3, 10, 30, and 60  $\mu$ M, respectively compared to 0.4% inhibition by the vehicle (0.3% DMSO in HEPES-buffered saline). The  $IC_{50}$  for SAM was 28.19  $\mu$ M, indicating weak hERG channel blocking activity. The ability of the major human metabolite RDC-9986 to inhibit the hERG potassium current was investigated in a separate GLP assay using two concentrations of RDC-9986, 9.32 and 280  $\mu$ M. The hERG current was only inhibited by 1.9% and 0.9%, respectively compared to 1.3% for the vehicle, indicating minimal hERG inhibition by RDC-9986. The 2nd major human metabolite RDC-0166 was not evaluated in the hERG assay since it was identified after completion of the thorough human QT study.

SAM was evaluated for cardiovascular endpoints including QT-interval, QRS duration, the monophasic action potential duration at 60% repolarization (MAPD60), and

measures of contractility (left ventricular pressure [LVP], maximum rate of relaxation [dP/dTmin], and maximum rate of contraction [dP/dTmax]) in a non-GLP isolated perfused rabbit heart (Langendorff assay). SAM statistically significantly prolonged the QT interval by 10.1% to 10.8%, increased the QRS complex duration up to 34.4%, decreased dP/dTmin (up to 38.0%) and dP/dTmax (up to 27.3%) at 50  $\mu$ M compared to vehicle.

The in vivo cardiovascular effects of SAM were investigated in conscious telemetered beagle dogs administered single oral gavage doses of SAM at 0, 0.5, 3, and 10 mg/kg. At 10 mg/kg, SAM caused a reduction in systolic blood pressure, a slight but statistically significant increase in the QT interval (9 msec) and a decrease in dP/dTmax. Other changes at this dose level, which were not statistically significant, included a slight increase in heart rate and a decrease in mean pressure. The findings were not considered to be adverse; therefore, the NOAEL for in vivo cardiovascular effects in dogs is 10 mg/kg. The NOAEL dose provides nonclinical to clinical exposure multiples of approximately 20, 63, and 21 times for SAM, RDC-9986, and RDC-1066, respectively compared to the exposures at the MRHD of 10 mg SAM based on AUC in male and female dogs combined. Exposure data were estimated from a 5-day bridging toxicokinetic study (AT-0313-43) in dogs.

#### Respiratory:

Respiratory function was assessed in beagle dogs in the same GLP cardiovascular study above using single oral doses up to 10 mg/kg. There were no SAM-related effects on any respiratory parameter (respiratory rate, tidal and minute volume), therefore the NOEL was the highest dose tested of 10 mg/kg. The NOEL dose provides nonclinical to clinical exposure multiples of approximately 20, 63, and 21 times for SAM, RDC-9986, and RDC-1066, respectively compared to the exposures at the MRHD of 10 mg SAM based on AUC in male and female dogs combined.

## **5 Pharmacokinetics/ADME/Toxicokinetics**

### **5.1 PK/ADME**

#### Bioanalytical Methods

Validated (or qualified) bioanalytical methods that utilized liquid chromatography/tandem mass spectrometry (LC-MS/MS) analysis were used across nonclinical studies to quantify OLZ, SAM, and metabolites of SAM (RDC-9986 and RDC-1066) in mouse, rat, rabbit, dog, and monkey plasma, as well as in monkey urine.

#### Samidorphan (SAM):

This review focuses on nonclinical studies conducted by the Applicant which characterized the pharmacokinetic/toxicokinetic profile of SAM and its metabolites, and the toxicokinetic profile of the combination of OLZ and SAM.

#### Absorption

Systemic absorption was evaluated in several single-dose pharmacokinetic (PK) studies in Sprague-Dawley rats, Beagle dogs, and Cynomolgus monkeys administered SAM by

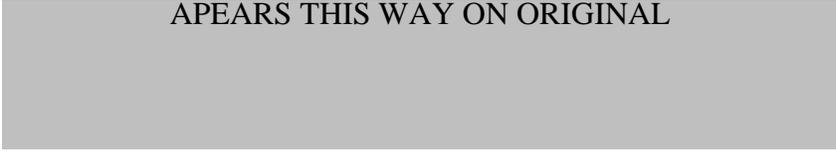
the oral, intravenous (IV), and subcutaneous (SC) routes. Absorption was also evaluated in four nonclinical studies in rats or dogs administered single oral doses of [<sup>14</sup>C]-SAM. In addition, GLP toxicokinetic (TK) bridging studies were conducted in rats, dogs, New Zealand rabbits, and CD-1 mice administered daily for 5 or 14 days in order to further characterize TK parameters of SAM and metabolites RDC-9986 and RDC-1066 used in general toxicity, reproductive toxicity, and carcinogenicity studies. However, CD-1 mice were not used in the mouse carcinogenicity study, but rather Tg.ras.H2 mice. Absolute bioavailability of SAM was determined to be 15% in rats after oral administration and 44% after subcutaneous (SC), administration of 10 mg/kg and 0.1 mg/kg respectively. Absorption was rapid with  $T_{max}$  values ranging between 0.25 and 1 hours after oral administration and 1 hour after SC administration. The elimination half-life was variable across acute toxicity studies in rats and ranged between 1 and 8 hours after single-dosing; values were more consistent in longer duration studies (i.e., 6-months) with  $t_{1/2}$  values of approximately 1 to 2 hours. There was a clear sex difference in exposure to SAM and metabolite RDC-1066 after oral administration to rats, with females having 3- to 8-fold higher exposure to SAM (based on AUC) compared to males at equivalent doses. The effect was more pronounced at lower doses; females showed much less exposure and  $C_{max}$  values than males across doses (table below). In dogs, oral bioavailability was greater than in rats, ranging between 39% to 66%. Absorption was also rapid with  $T_{max}$  values ranging between 0.25 and 1 hour after oral dosing, and the elimination half-life ranged from 2 to 3 hours after oral dosing.

Unlike in rats, there was no significant sex difference in exposure to SAM and metabolites in dogs, therefore exposure values were combined when displayed in tables. Oral bioavailability was greatest in monkeys at 70%, however monkeys were not used in general toxicity studies due to a high degree of first pass metabolism, the

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elimination half-life of SAM in monkeys ranged between 4 and 7 hours. Note that TK

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parameters were assessed in fed rats but in fasted dogs.

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Exposure increased approximately dose-proportional at lower doses in rats and dogs, and greater than dose-proportional at the higher doses used in toxicity studies. Exposure was approximately dose-proportional in rabbits at all doses used in the embryofetal development study. There was minimal accumulation of SAM or metabolites (accumulation ratios < 2) after repeated oral dosing to rats, dogs, and rabbits.

**Table 6: 14-day oral gavage toxicokinetics of SAM and metabolites in rats**

**4.2. 14-Day Oral Gavage Toxicokinetic Study in Rats (AT-0313-41)**

Test Article: RDC-0313-02											
Species	Rat										
Study No.:	AT-0313-41										
Feeding condition:	Fed										
Sample (eg, whole blood, plasma, serum):	Plasma										
Analyte:	RDC-0313, RDC-9986, and RDC-1066										
Assay:	LC-MS/MS										
Number of Animals/Gender:	14/sex/dose										
Vehicle/Formulation:	Sterile water										
Route of Administration:	PO										
Dose (mg/kg):	25		50		100		250		350		
Study Day:	1	14	1	14	1	14	1	14	1	14	
PK parameters (Males):											
RDC-0313	C <sub>max</sub> (ng/mL)	679	671	1690	1860	4170	3390	10200	9890	12400	10800
	t <sub>max</sub> (hr)	0.25	0.5	0.5	1	0.5	0.5	0.5	1	0.25	1
	AUC <sub>0-24</sub> (hr*ng/mL)	1100	1720	3800	4760	11400	14300	36500	56000	63500	71400
	t <sub>1/2</sub> (hr)	8.61	1.66	NA <sup>a</sup>	4.26	2.53	NA <sup>a</sup>	3.20	NA <sup>a</sup>	2.71	NA <sup>a</sup>
RDC-9986	C <sub>max</sub> (ng/mL)	2850	1580	3670	2250	5870	4310	9980	7190	12200	8680
	t <sub>max</sub> (hr)	0.5	1	1	1	2	2	4	4	4	4
	AUC <sub>0-24</sub> (hr*ng/mL)	9410	8030	16400	12400	36600	33500	88000	89000	135000	110000
	t <sub>1/2</sub> (hr)	3.67	3.32	3.66	4.89	3.13	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	4.66	NA <sup>a</sup>

Dose (mg/kg):		25		50		100		250		350	
Study Day:		1	14	1	14	1	14	1	14	1	14
<b>PK parameters (Males): (continued)</b>											
RDC-1066	C <sub>max</sub> (ng/mL)	30.4	22.6	48.4	33.2	109	50.2	93.9	89.9	108	101
	t <sub>max</sub> (hr)	0.25	0.5	0.25	1	0.25	0.5	0.5	0.5	0.25	0.5
	AUC <sub>0-24</sub> (hr*ng/mL)	37.4	62.0	99.5	96.2	206	224	399	500	559	781
	t <sub>1/2</sub> (hr)	2.13	2.26	1.10	3.80	1.54	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	4.96	NA <sup>a</sup>
<b>PK parameters (Females):</b>											
RDC-0313	C <sub>max</sub> (ng/mL)	3540	3370	4520	4120	7270	7690	18400	18100	23200	20500
	t <sub>max</sub> (hr)	0.25	1	0.25	1	0.25	1	2	2	4	4
	AUC <sub>0-24</sub> (hr*ng/mL)	9350	10600	21000	23300	50200	57500	201000	185000	266000	264000
	t <sub>1/2</sub> (hr)	2.30	3.71	2.06	NA <sup>a</sup>	2.87	5.18	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>
RDC-9986	C <sub>max</sub> (ng/mL)	642	560	584	485	698	633	2100	2070	3570	1950
	t <sub>max</sub> (hr)	0.5	0.5	2	2	0.5	2	4	1	2	4
	AUC <sub>0-24</sub> (hr*ng/mL)	2750	2330	4040	3620	6840	6990	22900	24900	24900	28000
	t <sub>1/2</sub> (hr)	3.46	4.24	3.00	NA <sup>a</sup>	4.63	NA <sup>a</sup>				
RDC-1066	C <sub>max</sub> (ng/mL)	53.7	38.1	45.4	40.0	85.4	55.1	87.3	113	103	119
	t <sub>max</sub> (hr)	0.25	1	1	1	0.25	2	0.5	1	0.5	0.5
	AUC <sub>0-24</sub> (hr*ng/mL)	155	146	224	260	525	543	993	1220	1280	1510
	t <sub>1/2</sub> (hr)	1.59	3.63	2.52	NA <sup>a</sup>	3.80	9.89	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>

Abbreviations: NA=not applicable; PK=pharmacokinetic; PO=oral

<sup>a</sup> Not reported due to an adjusted R<sup>2</sup> less than 0.9.

## [NDA 213378, Pharmacokinetics Tabulated Summary]

**Table 7: 5-day oral gavage toxicokinetics of samidorphan and metabolites in dogs****4.4. A 5-Day Oral Gavage Toxicokinetic Study in Beagle Dogs (AT-0313-43)**

Species:	Dog						
Study No.:	AT-0313-43						
Feeding condition:	Fasted						
Sample (eg, whole blood, plasma, serum):	Plasma						
Analyte:	RDC-0313, RDC-9986, and RDC-1066						
Assay:	LC-MS/MS						
Number of Animals/Gender:	3M/3F/dose						
Vehicle/Formulation:	Sterile water						
Route of Administration:	PO						
Dose (mg/kg):	1		3		10		
Study Day:	1	5	1	5	1	5	
<b>Mean ± SD PK parameters:</b>							
RDC-0313	C <sub>max</sub> (ng/mL)	167 ± 45.6	123 ± 41.7	482 ± 198	337 ± 73.3	1840 ± 327	1950 ± 182
	t <sub>max</sub> (hr) <sup>a</sup>	1	0.25	NA	NA	0.25	NA
	AUC <sub>0-24</sub> (hr*ng/mL)	634 ± 216	563 ± 163	1460 ± 385	1490 ± 314	7320 ± 4260	9500 ± 3550
	t <sub>1/2</sub> (hr)	1.81	2.26	1.79	2.43	2.91	3.03
RDC-9986	C <sub>max</sub> (ng/mL)	124 ± 21.5	105 ± 11.4	402 ± 130	342 ± 57.9	1050 ± 222	1240 ± 259
	t <sub>max</sub> (hr) <sup>a</sup>	NA	2	1	2	NA	NA
	AUC <sub>0-24</sub> (hr*ng/mL)	1310 ± 111	1300 ± 85.3	3920 ± 797	3640 ± 599	11800 ± 1070	12900 ± 2680
	t <sub>1/2</sub> (hr)	7.31	7.18	7.72	7.88	6.93	7.43

Study No. AT-0313-43							
Dose (mg/kg):		1		3		10	
Study Day:		1	5	1	5	1	5
Mean ± SD PK parameters: (continued)							
RDC-1066	C <sub>max</sub> (ng/mL)	34.9 ± 4.33	24.3 ± 5.71	75.5 ± 26.5	69.2 ± 15.6	256 ± 67.6	314 ± 99.5
	t <sub>max</sub> (hr) <sup>a</sup>	1	1	1	2	1	1
	AUC <sub>0-24</sub> (hr*ng/mL)	131 ± 25.9	119 ± 29.1	301 ± 62.9	319 ± 68.8	1310 ± 334	1690 ± 346
	t <sub>1/2</sub> (hr)	1.91	2.24	1.78	1.96	2.54	2.86

Abbreviations: F=female; M=male; NA=not applicable; PK=pharmacokinetic; PO=oral; SD=standard deviation

<sup>a</sup> Median.

## [NDA 213378, Pharmacokinetics Tabulated Summary]

### Distribution

Plasma protein binding of SAM and the 2 metabolites was low in human plasma and across animal species. Values in human plasma ranged between 23% to 33% bound across all concentrations tested and were more variable, across nonclinical species, not exceeding 60% bound, and generally increased with increasing drug concentration: 45%, 50%, 60%, and 12% in mouse, rat, dog, and monkey plasma (male animals), respectively. Plasma protein binding of the N-dealkylated metabolite (RDC-9986) was low in human plasma, 10% to 20%, and lower across nonclinical species: 12%, 13%, 7%, 5%, and 7% in mouse, rat, rabbit, dog, and monkey plasma, respectively. Plasma protein binding of the N-oxide metabolite of SAM (RDC-1066) was low, but not as low as RDC-9986, in human plasma and nonclinical species: 25% to 37% in human plasma, and 31%, 36%, 37%, 33%, and 33% in mouse, rat, rabbit, dog, and monkey plasma, respectively.

The distribution of SAM into red blood cells was evaluated in male Long-Evans rats and in male and female beagle dogs after single oral administration (3 mg/kg [<sup>14</sup>C]-SAM). Blood:plasma ratio was approximately 1, indicating some partition to red blood cells, in male rats as early as 0.5 hours following dosing, but was below the limit of quantification at 72 hours post-dose. SAM had a greater amount of partitioning to red blood cells in dogs compared to rats, with blood:plasma ratios of approximately 2 in both males and females 1 hour after dosing and reaching a maximum of 2.9 in males and 2.6 in females 24 hours after dosing.

SAM was detected in cerebral spinal fluid (CSF) of cynomolgus monkeys (n=4) following both intravenous (1 mg/kg) and oral administration (3 mg/kg) with maximal exposure reached by 4 hours after administration. Exposure to SAM was slightly higher in CSF compared to plasma following intravenous administration and approximately equal following oral administration indicating good CSF penetration.

Tissue distribution was evaluated in two studies in rats administered single oral doses of 10 mg/kg [<sup>14</sup>C]-SAM. In the first study using male and female Sprague-Dawley rats, only a select number of tissues were evaluated for radioactivity, with the greatest amount of radioactivity detected in liver, stomach, small, and large intestines, with females showing lower amounts in the liver and higher amounts in the stomach compared to males. The second study was a whole-body autoradiography study conducted in male Long-Evans rats.

The highest amount of radioactivity was detected in the following organs in descending order: uveal tract, eye, urinary bladder wall, liver, kidney medulla, pituitary gland, and pancreas. Tissue:plasma ratios were greater than 1 except brain and spinal cord the ratio was less than 1. Peak concentrations were reached between 0.5 and 2 hours postdose for most tissues, except for the eye, lens, and uveal tract in which peak concentrations were reached at 6 hours postdose. At 672 hours (28 days), postdose, only the uveal tract and eye had measurable amounts of radioactivity. Mean concentrations of radioactivity were lower in non-pigmented skin compared to pigmented skin at 6 hours postdose through 120 hours postdose. These data suggest binding to melanin.

### Metabolism

There are two major circulating human metabolites of SAM measured at greater than 10% of total drug-related exposure based on radioactivity, RDC-9986 (N-dealkylated metabolite) and RDC-1066 (N-oxide), comprising approximately 18% and 17% of total radioactivity in plasma respectively (study 33-B107). Both metabolites are formed in rats, dogs, CD-1 mice, and rabbits in vivo. Metabolite RDC-1066 was discovered in human plasma late in clinical development and was not measured in initial nonclinical toxicity studies. Therefore, a series of nonclinical GLP PK bridging studies were conducted in rats, mice, dogs, and rabbits administered oral doses of SAM for 5 to 14 consecutive days at doses that covered the doses used in pivotal chronic repeat-dose toxicity studies, reproductive and development studies, and carcinogenicity studies. Data from these studies indicated that there is adequate exposure coverage, as measured by AUC, for the major human metabolites RDC-9986 and RDC-1066 in at least one animal species and doses used in general toxicity, reproductive toxicity, and the rat 2-year carcinogenicity study compared to exposures in humans at the maximum recommended human dose 10 mg SAM ([see table 10, section 11](#)).

In vitro studies revealed that SAM is primarily metabolized to RDC-9986 by CYP3A4 and, to a lesser extent, by CYP3A5 and 2C19, while RDC-1066 is primarily formed by CYP3A4 and to a lesser extent CYP3A5 and 2C8. SAM was very stable in human, dog, or monkey hepatocytes undergoing very little metabolic degradation in vitro, while it was unstable and underwent extensive metabolic degradation in male rat and mouse hepatocytes and microsomes. SAM is believed to undergo enterohepatic recirculation in the monkey.

Metabolites RDC-9986 and RDC-1066 are both formed in vivo in mice, rats, dogs, and rabbits. After repeated (5 days) dosing of SAM to dogs, exposure to RDC-9986 ranged from 145% to 252% of parent drug in both males and females, with little sex difference in plasma exposure. After repeated (5 to 14 days) dosing in male mice and rats, exposure to RDC-9986 ranged from 154% to 455% of parent drug. In contrast, in female rodents, systemic exposure for RDC-9986 was less than that of SAM, with exposures to RDC-9986 ranging from 11% to 44% of parent drug. RDC-1066 is a minor metabolite in mice and rats (ranging from <1% to 5% of parent AUC). RDC-1066 was formed more extensively in rabbits and dogs (46% to 71% and 22% of exposure to parent, respectively). In humans, based on AUC at steady-state, exposure to RDC-9986 was approximately equal to that of parent drug, while exposure to RDC-1066 was only

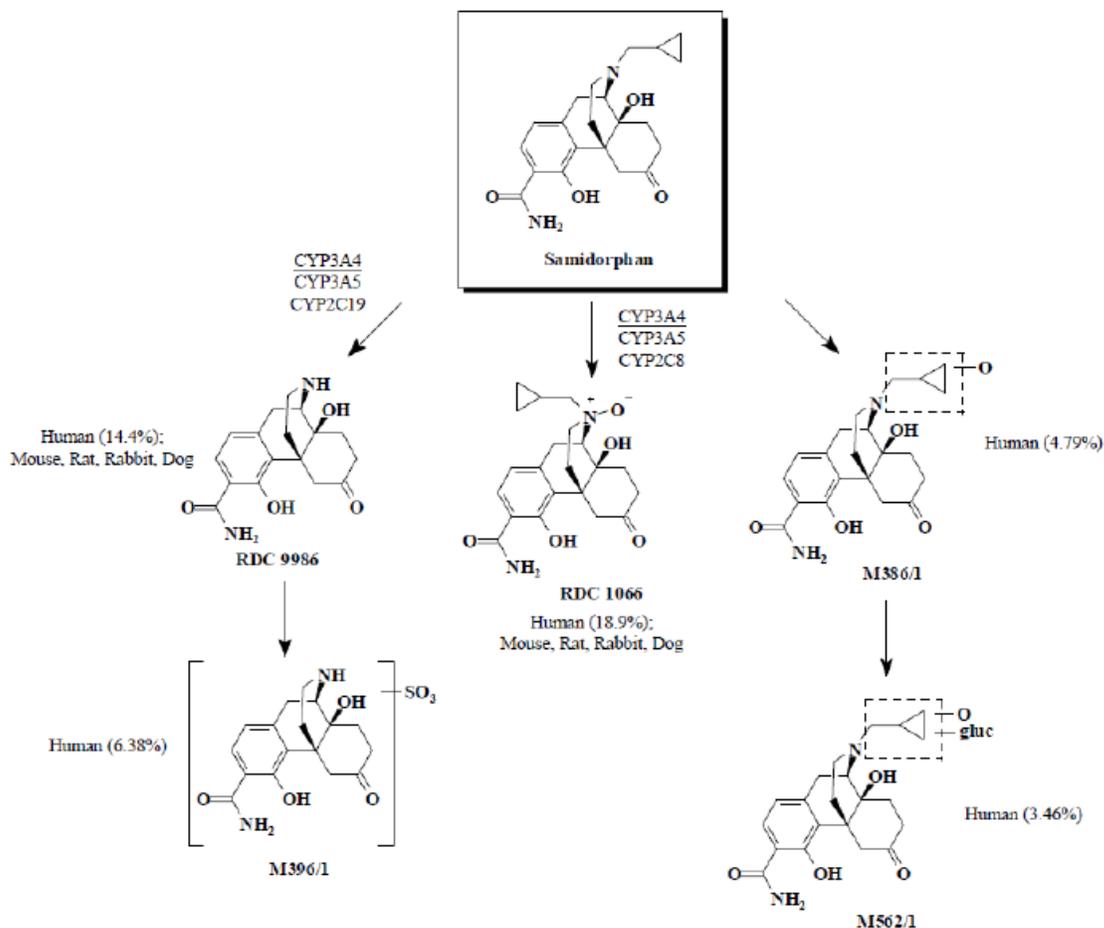
about 21% of parent drug. Metabolite to parent drug exposure ratios in humans are more similar to dogs than to rodents.

The  $t_{1/2}$  values for RDC-9986 were longer than that of SAM, approximately 3 to 4 hours and 7 to 8 hours in rats and dogs, respectively, compared to a  $t_{1/2}$  for SAM of 1 to 2 hours in rats and 2 to 3 hours for dogs. The  $t_{1/2}$  for RDC-1066 was generally similar to that of SAM in dogs, ranging from 1.8 to 2.9 hours, but was more variable in rats, ranging from 1.1 to 9.9 hours.

Sex differences in metabolism were observed in rats in vitro and in vivo. There was a 10-fold greater formation of metabolite RDC-9986 in liver microsome preparations from male rats compared to females, and a 3- to 5-fold greater exposure to RDC-9986 in vivo in male rats compared to female rats. No sex difference in metabolism was identified in dogs. The overall metabolic profile in dogs is most similar to humans, which is one reason why the nonclinical combination toxicity study of OLZ and SAM was conducted in dogs as opposed to rats.

As noted in the pharmacology section of the review, both major human metabolites, RDC-9986 and RDC-1066, bind with relatively high affinity to mu-opioid receptors, and less to kappa- and delta-opioid receptors. In vitro, RDC-9986 functions as a mu-opioid agonist. In vitro functional activity assays were not conducted with RDC-1066. In vivo rodent behavioral assays conducted with RDC-9986 indicated that RDC-9986 may function as a partial opioid agonist.

**Figure 4: Proposed metabolic pathway of samidorphan**



Abbreviation: gluc=glucuronide.

Notes: %=percent total radioactivity in human plasma following a 2 mg SL single dose of [<sup>14</sup>C]-SAM (based on pooled AUC<sub>0-8hr</sub> sample); human exposure quantified after oral dosing is similar. Primary metabolizing enzymes indicated by underlined text.

Source: Adapted from ALK33-B107 metabolite ID report (Table 8 and Figure 21); primary metabolizing enzymes based on AM-0313-07 and AM-0313-21.

[Source: NDA 213378, Pharmacokinetics Written Summary]

**Table 8: Comparison of Metabolite Exposure and Metabolite to Parent Ratios across Nonclinical Species and Humans at Steady-State**

Species (N); Study No.	Study Day	Dose <sup>a</sup>	Sex	AUC <sub>0-24</sub> (hr*ng/mL)		Metabolite:Parent Ratio <sup>b</sup>	
				RDC-9986	RDC-1066	RDC-9986	RDC-1066
Mice (N=36/sex/group) AT-0313-42	Day 5	125 mg/kg SAM	M	26500	282	455%	4.9%
			F	14700	1010	41.7%	2.9%
		500 mg/kg SAM	M	94500	1800	219%	4.2%
			F	57000	4360	44.0%	3.4%
Rats (N=12/sex/group) AT-0313-41	Day 14	25 mg/kg SAM	M	8030	62.0	467%	3.6%
			F	2330	146	21.9%	1.4%
		350 mg/kg SAM	M	110000	781	154%	1.1%
			F	28000	1510	10.6%	0.6%
Rabbits (N=3 F/group) AT-0313-40	Day 5	10 mg/kg SAM	F	996	2330	30.3% (40.6%)*	71.3% (95.9%)*
		90 mg/kg SAM	F	12100	27900	20.0% (23.9%)*	46.2% (54.9%)*
Dogs (N=6/group) AT-0313-43	Day 5	1 mg/kg SAM	M & F	1300	119	252%	21.5%
		10 mg/kg SAM	M & F	12900	1690	145%	19.0%
Humans (N=42) ALK3831-A104	Day 14	ALKS 3831 10/10 or ALKS 3831 20/10 <sup>c</sup>	M & F	225	61.2	62.5%	17.0%

Abbreviations: BUP=buprenorphine; F=female; M=male; SAM=samidorphan; TK=toxicokinetic.

<sup>a</sup> Low and high doses evaluated in TK bridging studies are presented.

\* Mean Metabolite:Parent ratio values in parentheses are corrected for RDC-1066 interference on SAM concentrations. Day 5 SAM AUC values have been reduced by 26%, 24%, and 16% for the 10, 30, and 90 mg/kg/day groups, respectively, compared to the original mean SAM AUC values reported in Study AT-0313-40. Corrected values are reported to 3 significant figures. See Section 4.2.2.1 RDC-1066 Cross-assay Interference Nonclinical Evaluation Summary for details.

<sup>b</sup> Reported as percentage of parent AUC.

<sup>c</sup> One oral bilayer tablet daily containing 10 mg OLZ and 10 mg SAM (referred to as ALKS 3831 10/10) or one oral bilayer tablet daily containing 20 mg OLZ and 10 mg SAM (referred to as ALKS 3831 20/10).

[Source: NDA 213378, Pharmacokinetics Written Summary]

### Excretion

The elimination/excretion profile of SAM was evaluated in mass balance studies using [<sup>14</sup>C]-SAM orally administered to Sprague-Dawley rats and Beagle dogs, 10 mg/kg and 3 mg/kg, respectively, as well as in a PK study with SAM in male and female monkeys. In rats, 88% of the administered dose was recovered over 48 hours, with most of the radioactivity excreted in urine followed by feces with 65% and 18% of the administered dose, respectively. Metabolite RDC-9986 accounted for 61% of the administered dose present in the 24-hour urine sample, while SAM accounted for only a fraction of the administered dose (0.90%). RDC-9986 was the major radioactive component in feces (24% of the administered dose), while SAM was not detected in feces. The excretion profile of [<sup>14</sup>C]-SAM was only evaluated in male rats, however metabolism of SAM is very different in male rats compared to female rats.

In dogs, approximately 90% of the administered dose was recovered in urine over 48 hours with 69% of the administered dose for males and 78% for females, followed by feces with 15% of the administered dose for males and 13% for females. In the collected urine samples, metabolite RDC-9986 accounted for 49% of the administered dose for males and 63% for females, while SAM accounted for 14% administered dose for males and 9% for female dogs. Excretion of metabolite RDC-1066 was not measured in the first mass balance studies conducted in rats and dogs, therefore follow-up PK and metabolite profile studies were using a single oral dose of [<sup>14</sup>C]-SAM (50 mg/kg and 10 mg/kg, in rats and dogs, respectively). However, in those studies, metabolite RDC-1066 was not detected in plasma compared to the reference standard.

A mass balance study was not conducted in monkeys, but a single-dose PK study comparing intravenous (1 mg/kg) and oral (1, 3, and 10 mg/kg) and measuring urine excretion was conducted. Unchanged SAM in the collected urine was minimal (5% to 8% of the recovered dose). Renal clearance accounted for approximately one-third of total clearance, indicating that non-renal clearance of SAM (i.e., metabolism) is the major route of elimination in monkeys.

A dedicated study to determine if SAM and/or its metabolites is secreted into milk of lactating animals was not conducted. However, when SAM was orally administered to pregnant and lactating rats in a pre- and postnatal development study, SAM and metabolite RDC-9986 were detected in the plasma of nursing pups indicating the potential for SAM and its metabolites to be secreted into milk.

#### Olanzapine+Samidorphan:

Pharmacokinetics of co-administration of OLZ and SAM was evaluated in two repeat-dose toxicity studies in Beagle dogs, a non-GLP escalating-dose study 21-day repeated-dose tolerance study (study no. AT-0313-33) and a GLP 13-week repeated-dose toxicity study (study no. AT-0313-34), and in pregnant Sprague-Dawley rats in a dose range-finding (study AT-0313-44) and a definitive (study AT-0313-45) embryofetal development toxicity studies.

In dogs, the addition of OLZ did not have any significant effect on exposure or TK parameters of SAM or RDC-9986, including  $T_{max}$  and  $T_{1/2}$ , compared to SAM administration alone. However, in the 21-day repeat-dose tolerance study in dogs, systemic exposures of OLZ and the N-desmethyl metabolite of OLZ were slightly lower in the presence of 10 mg/kg/day SAM compared to OLZ alone. Although, a similar increase in OLZ exposure with the co-administration of SAM was not observed in the 13-week repeat-dose combination toxicity study which studied a larger number of animals (5/sex compared to only 2/sex in the 21-day study) (the N-desmethyl metabolite of OLZ was not measured in that study).

In pregnant rats, plasma exposure for SAM, RDC-9986, and RDC-1066 were similar following daily oral administration of SAM in combination with OLZ when compared with

same dose of SAM alone, and similarly plasma exposure to OLZ did not significantly change following repeated administration of SAM in combination with OLZ.

SAM and OLZ did not affect the metabolism of each other in vitro. The inhibitory potential of SAM and OLZ were investigated in a non-GLP in vitro study using human liver microsomes (study no. AM-0313-11). SAM or OLZ (0.1  $\mu\text{M}$ ) was incubated with or without increasing concentrations of the other compound (OLZ or SAM) (0.05, 0.1, 1, or 10  $\mu\text{M}$ ) for up to 120 minutes. Levels of the primary metabolite of SAM, RDC-9986 generated ranged from 2.7% to 5.6% and increasing concentrations of OLZ did not significantly affect the level of RDC-9986 metabolite formed. Levels of the desmethyl metabolite of OLZ ranged from 1.97% to 3.81% and increasing concentrations of SAM did not significantly affect the level of the OLZ-metabolite formed.

Nonclinical studies investigating the distribution, in vivo metabolism, and excretion of the combination of OLZ and SAM were not conducted.

#### Other pharmacokinetic studies:

The Applicant conducted an evaluation of potential cross-analyte interference of metabolite RDC-1066 due to the need to estimate RDC-1066 exposure levels in the completed toxicology studies based on results from GLP bridging toxicokinetic studies in mice, rats, rabbits, and dogs (“RDC-1066 Cross-Assay Interference Nonclinical Evaluation Summary”). The report investigated interference from RDC-1066, and its impact on reported concentrations and TK parameters of SAM and RDC-9986. The report concluded that there was no interference of RDC-1066 for quantification of OLZ across all assays. There was significant interference by RDC-1066 for quantification of SAM and RDC-9986 in all species, potentially due to its conversion to either SAM and/or RDC-9986 during sample extraction step for the assay. A comprehensive evaluation was conducted for all assays at multiple concentrations of RDC-9986, and RDC-1066 to cover the range of plasma exposures reported in the toxicology studies. The results indicated no significant interference for mouse, rat, or dog plasma assays. However, in rabbit, for SAM, the individual plasma concentration ratios of RDC-1066:SAM for the majority of samples from the TK bridging study (AT-0313-40) ranged between 0.3:1 to 0.9:1. *“The impact of this interference on TK parameter estimation was evaluated by applying appropriate correction factors based on the SAM concentration and the RDC-1066:SAM concentration ratio in each sample. The results from the TK analysis with the corrected SAM concentrations was used to calculate exposure multiples for the GLP embryo-fetal development study in rabbit (AT-0313-23).”*

## **6 General Toxicology**

All tables and figures excerpted from Applicant’s study reports unless stated otherwise.

### **6.1 Single-Dose Toxicity**

**Study Title:** A Single-Dose Toxicity and Toxicokinetic Study of RDC-0313-02 when Administered via Oral Gavage to Sprague Dawley Rats (AT-0313-03)

Sprague Dawley rats were administered 35, 110, or 350 mg/kg of RDC-0313-02 once by oral gavage. Necropsy was scheduled for days 2 and 15. N=10/sex/group TK satellite cohort. Toxicity parameters: clinical observations, body weight, food consumption, ophthalmic examinations, and clinical and anatomic pathology, including organ weights, organ weight ratios, and histopathology. The only notable toxicity was a transient decrease in body weight for high dose females. The NOAEL was determined to be the highest dose of 350 mg/kg/day for males and females.

**Text Table 1. TK Parameters for RDC-0313 in Plasma following a Single Gavage Administration to Rats**

Gender	Target Dose (mg/kg)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	Elim Rate Constant (hr <sup>-1</sup> )	Elim Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*µg/mL)	AUC <sub>∞</sub> (hr*µg/mL)
Male	35	2.93	0.250	0.356	1.95	13400	37500	2.61	2.62
	110	7.31	0.250	0.0852	8.13	6600	77400	16.5	16.7
	350	23.7	0.250	0.209	3.31	6460	30900	53.8	54.2
Female	35	7.48	0.250	0.336	2.06	1960	5830	17.9	17.9
	110	13.9	0.250	0.198	3.51	1750	8860	62.5	62.8
	350	31.0	1.00	0.113	6.12	1270	11200	256	275

**Study Title:** Bioavailability, Toxicokinetic, and 5-Day Repeated Dose Study of RDC-313-02 in Dogs (AT-0313-02)

Three male and female beagle dogs were administered a single intravenous bolus injection and a single oral gavage dose of 1 mg/kg for the bioavailability phase of the study. The same dogs then received a single oral gavage dose at 3, 10, 20, and 40 mg/kg for the maximum tolerated dose phase of the study. Study endpoints included observations, body weights, hematology, and serum chemistry determinations, and blood samples for toxicokinetics after each dose. Clinical signs including excessive salivation, hypoactivity, and tremors (4 hrs post dose), were observed in animals at doses ≥10 mg/kg and, pupil dilation was also observed at the high dose of 40 mg/kg. Oral bioavailability after the 1 mg/kg dose was 66%. The maximum tolerated dose (MTD) was >40 mg/kg.

**Text Table 9. An Overall Summary of RDC-0313 Pharmacokinetic Parameters**

Route	Target Dose (mg/kg)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>a</sup> (hr)	AUC <sub>(∞)</sub> (ng*hr/mL)	T <sub>½</sub> (hr)	CL or CL/F <sup>b</sup> (mL/hr/kg)
Intravenous	1	N/A	N/A	774 (140)	1.9 (0.5)	1330 (248)
Oral	1	107 (14.1)	1.0 (1.0-2.0)	510 (160)	2.4 (0.7)	2124 (641)
Oral	3	303 (104)	1.0 (0.25-4.0)	1776 (743)	3.3 (1.2)	1943 (758)
Oral	10	1840 (323)	1.0 (1.0-2.0)	8702 (1323)	3.2 (1.6)	1173 (187)
Oral	20	3057 (1308)	1.0 (0.5-1.0)	12896 (5250)	2.7 (0.4)	1773 (683)
Oral	40	6987 (3086)	0.5 (0.25-1.0)	33127 (16151)	4.7 (2.1)	1631 (1082)

a. Median and (range).

b. Clearance (CL) for intravenous route; for oral route, clearance/fraction of administered dose absorbed (CL/F).

## 6.2 Repeat-Dose Toxicity

### 6.2.1.1 Rat Sub-chronic

Sub-chronic repeat-dose toxicity studies conducted in rats include a 2-week oral toxicity study with a 2-week recovery period at doses of 35, 110 and 350 mg/kg/day, and a 13-week oral toxicity study with a 4-week recovery period at doses of 25, 75 and 250 mg/kg/day; these studies were adequate (study nos. AT-0313-07 and AT-0313-18, respectively). SAM was tolerated in rats up to the maximum feasible dose based on solubility of 350 mg/kg. There was no mortality in the 2-week study and only one death in the 13-week repeat-dose study that was not considered to be drug-related. The main toxicities observed in both studies were decrease in body weight that correlated with decreased food intake. In the 2-week study, body weight was significantly decreased together with decrease in food consumption, and histopathological findings in the lungs, liver, and heart. In the 13-week study, there was a dose-related decrease in body weight in males only, up to 20% compared to controls, with a corresponding decrease in food consumption. Histopathological findings were observed in the kidney (nephropathy), heart (cardiomyopathy), and liver (hepatocellular hypertrophy) of male and female rats at 75 and/or 250 mg/kg/day. These effects were all fully reversible except for the liver findings in male, but there was evidence of partial reversibility. Other findings included changes in the pancreas (islet cell vacuolation) and teeth (dentin dysplasia and pulp cavity metaplasia) observed only in high dose males the relevance of both is unclear. The NOAEL in the 13-week rat study was 25 mg/kg/day for males and females, and the MTD was 75 mg/kg/day for males and 250 mg/kg/day for females due to dose-related decreases in body weight and food consumption for males only. These drug effects in males occurred even though exposure to parent drug were higher in females than in males (~10-fold) based on AUC. This difference could be due to a much higher clearance and volume of distribution and higher exposures to metabolite RDC-9986 in males compared to females (although metabolites were not measured in this study). Complete reviews for rat sub-chronic toxicity studies can be found under the INDs for SAM.

### 6.2.1.2 Rat 6-month

**Study title:** 26-week oral gavage toxicity study of RDC-0313 in Sprague-Dawley rats with a 4-week recovery period and an interim necropsy at 13 weeks

Study no.:	AT-0313-16
Study report location:	SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 12, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RDC-0313-02, Lot CMLW-225/09-AR4, 97.1%

## Key Study Findings

- Significant decrease in body weight in high dose males and females at 50 mg/kg/day, 24% and 9% compared to controls, respectively.
- Significant decrease in body weight for low and mid males, but not dose-related, (>10% compared to controls).
- Effects on body weight correlated with decreases in food consumption for males and females.
- Liver histopathology findings (hepatocellular cytoplasmic vacuolation) high dose males, partially reversible
- Sex differences in TK parameters (females had higher exposure levels due to higher clearance rates and larger volume of distribution in males compared to females).
- NOAEL = 5 mg/kg/day for males due to decrease body weight and liver findings and 5 mg/kg/day for females due to decrease body weight.
- Safety margins at the NOAEL are 0.4 and 5 times for males and females, respectively compared to exposure at the MRHD of 10 mg SAM based on AUC at steady state on day 182.

## Methods

Doses:	0, 0.5, 5, 50 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	Sterile water for injection
Species/Strain:	Rat/Sprague-Dawley from <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>
Number/Sex/Group:	40/sex/group (control and high dose) 30/sex/group (low and mid doses)
Age:	At dosing initiation: 8 to 9 weeks
Weight:	At dosing initiation: males 271-330 g and females 183-234 g
Satellite groups:	Toxicokinetics: 9/sex/group 10/sex/control and high dose kept for 4-week recovery period
Unique study design:	13-week interim sacrifice: 10 rats/group were necropsied on day 92. 20 rats/group were necropsied on day 183, and 10 rats/groups 1 and 4 were necropsied on day 211 (recovery groups)
Deviation from study protocol:	None that affected study integrity

## Observations and Results

### Mortality

There were no drug-related deaths. One control male was found dead on day 125; no cause of death was determined. One control TK male was found dead on day 182 following blood collection.

### **Clinical Signs**

There were no drug-related clinical signs. All clinical signs were incidental as they were not dose-related, and many were also observed in control animals. Observations for morbidity/mortality were made twice a day, at least 6 hours apart. Cage-side clinical observations were made twice daily; prior to dosing and 1 to 2 hours after dosing. Detailed clinical observations were made prior to dosing on day 1 and weekly throughout the study.

### **Body Weights**

There was a statistically significant decrease in mean body weight for males at 50 mg/kg/day throughout the entire dosing period compared to controls, with a maximum decrease of 24% on day 182/end of dosing. Mean absolute body weight was also decreased compared to controls at 0.5 and 5 mg/kg/day throughout most of the study, but not in a dose-related manner. There was a maximum decrease of 14% and 11% at 0.5 and 5 mg/kg/day compared to controls, respectively end of dosing. The effect on body weight for males was partially reversible as there was only a 6% decrease in mean body weight at the end of the 4-week recovery periods for high dose males compared to controls. Mean absolute body weight was also statistically significantly decreased for females in HD compared to controls, with a maximum decrease of 9% compared to controls end of dosing. Like males, the decrease in mean body weight for females at 0.5 and 5 mg/kg/day was not dose-related; there was a 6% and 4% decrease in body weight in low and mid dose groups compared to controls on day 182. The effect on body weight for females was partially reversible, as there was only a 7% decrease in mean body weight at the end of the 4-week recovery periods for high dose females compared to controls. The effects on body weight correlated with effects on food consumption for males and females. Body weights were recorded at least once pre-study, on dosing day 1, and weekly during the dosing period, and on the day prior to necropsy.

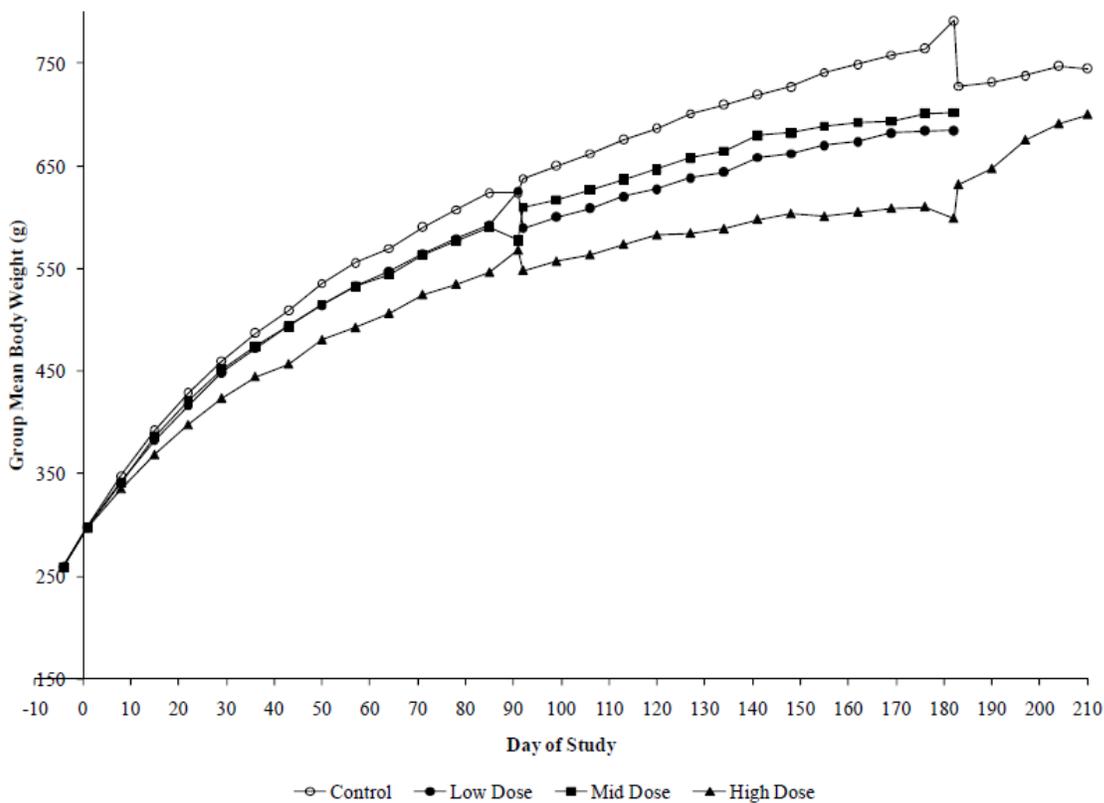


Figure 1. Group Mean Body Weight Data (g) – Core Toxicology Males

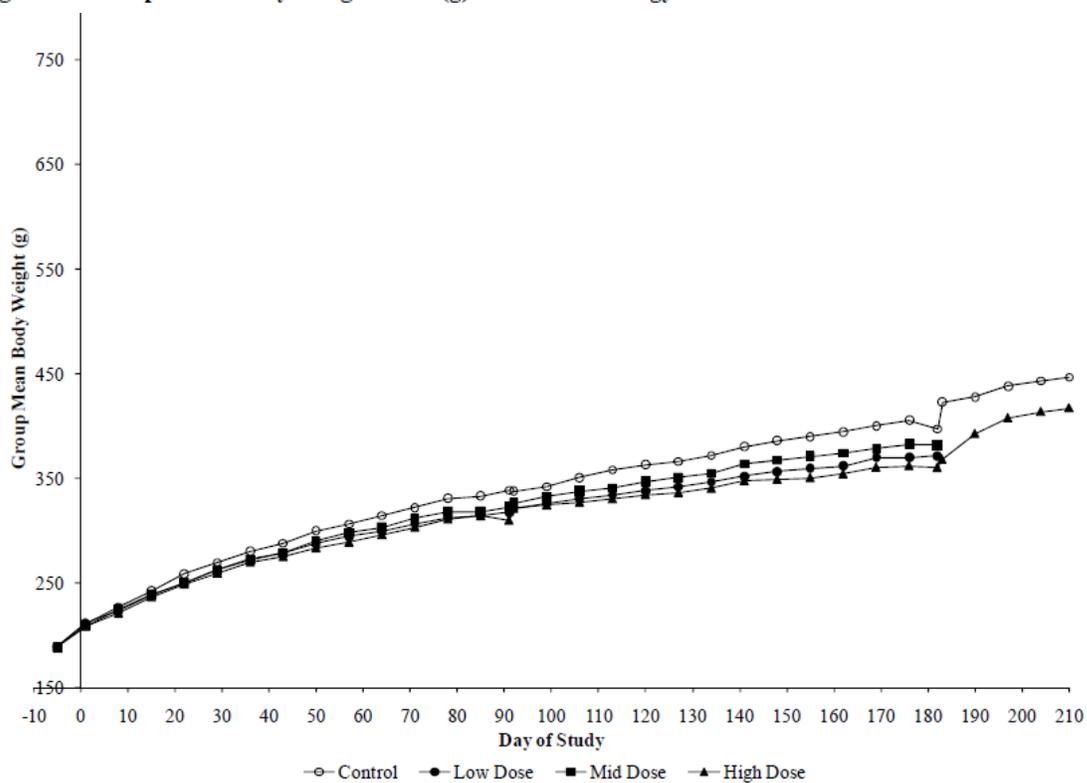


Figure 2. Group Mean Body Weight Data (g) – Core Toxicology Females

**Text Table 7. Percent Change in Body Weight Relative to Control Group – Core Toxicology Males**

Dose Group	Day 8	Day 85	Day 182	Day 210
0.5 mg/kg	-1.8	-5.1	-14	--
5 mg/kg	-2.0	-5.3	-11	--
50 mg/kg	-3.6	-12	-24	-6.1

**Text Table 9. Percent Change in Body Weight Relative to Control Group – Core Toxicology Females**

Dose Group	Day 8	Day 85	Day 182	Day 210
0.5 mg/kg	-1.4	-5.6	-6.5	--
5 mg/kg	-0.93	-4.5	-3.9	--
50 mg/kg	-2.6	-5.7	-9.3	-6.6

### Food Consumption

Group mean food consumption was consistently and statistically significantly lower for males at 50 mg/kg/day compared to controls throughout most of the dosing period, and for males at 5 mg/kg/day during the last few weeks of the dosing period. Food consumption for males at 0.5 mg/kg/day was comparable to controls for most of the dosing period. Food consumption for high dose females was statistically significantly decreased compared to controls for most of the dosing period. There was a significant decrease in food consumption for females at 5 mg/kg/day compared to controls during the last half of the dosing period. There was no consistent effect on food consumption for females at 0.5 mg/kg/day. During the 4-week recovery period, males and females at 50 mg/kg/day consumed significantly more food than controls. These effects on food consumption for the high dose males and females correlated with the effects on body weight. Food consumption was measured before dosing initiation, and weekly during the dosing period on the same days as body weight measurements.

### Ophthalmoscopy

Mild corneal crystals were observed in all groups, including controls, and not in a dose-related manner. The frequency of findings increased over duration of the study. The findings were not drug-related.

**Text Table 12. Summary of Rats with Mild Corneal Crystals (percent)**

Dose Group	Day 42	Day 87	Day 178	Day 206 (Males)/ 205 (Females)
<b>Males</b>				
Control	6/40 (15)	4/40 (10)	18/30 (60)	7/10 (70)
0.5 mg/kg	7/30 (23)	4/30 (13)	12/20 (60)	--
5 mg/kg	6/30 (20)	5/30 (17)	16/20 (80)	--
50 mg/kg	3/40 (8)	5/40 (13)	14/30 (47)	6/10 (60)
<b>Females</b>				
Control	6/40 (15)	3/40 (8)	22/30 (73)	8/10 (80)
0.5 mg/kg	6/30 (20)	4/30 (13)	16/20 (80)	--
5 mg/kg	11/30 (37)	4/30 (13)	15/20 (75)	--
50 mg/kg	7/40 (18)	3/40 (8)	18/30 (60)	9/10 (90)

Eye exams were conducted prior to group assignment, and on days 42, 87, 178, and 206 (males) or 205 (females).

### **Hematology, Clinical Chemistry, and Urinalysis**

There were no drug-related findings. There were several instances of statistically significant changes in drug-treated groups compared to controls, however the magnitude of change was small, and the values were within the historical control ranges for the laboratory. Blood samples were collected from main study animals on the day of scheduled necropsy. Urine was collected from overnight fasted animals on days 92, 183, or 211. Adequate batteries of hematology and coagulation, clinical chemistry, and urinalysis parameters were measured.

### **Gross Pathology**

One high dose male, 50 mg/kg/day, had a single pale focus in the liver at the day 92 necropsy which correlated microscopically to hepatocellular cytoplasmic vacuolation. All other macroscopic findings at the 92, 183, and day 211 necropsies were considered incidental and not drug-related.

### **Organ Weights**

There were several statistically significant increases in absolute organ weights compared to controls, but they were considered to be due to the decrease in terminal body weights in the drug-treated groups and not a direct effect on organ weights.

### **Histopathology**

There was an increase in incidence and severity of hepatocellular cytoplasmic vacuolation in the liver of high dose males (50 mg/kg/day) at the 92 day and 183 day necropsies compared to controls. The finding was partially reversible as only 3/10 high dose males were observed with hepatocellular cytoplasmic vacuolation in the liver compared to 1 control male and the severity was reduced compared to the day 92 and 183 necropsies. A similar finding was not observed in females.

Adequate Battery: Yes, tissues from the control, 0.5, and 50 mg/kg/day groups, as well as gross lesions and tissues from early death animals were examined microscopically by a board-certified veterinary pathologist.

Peer Review: Yes

Histological Findings

**Text Table 18. Microscopic Liver Findings with Average Severity – Males**

<b>Tissue/Observation</b>	<b>Dose Group (mg/kg):</b>	<b>0</b>	<b>0.5</b>	<b>5</b>	<b>50</b>
<b>Day 92</b>					
Liver	Number Examined:	10	10	10	10
	Hepatocellular Cytoplasmic Vacuolation	2	1	1	9
	Average Severity:	0.2	0.1	0.2	1.5
<b>Day 183</b>					
Liver	Number Examined:	19	20	20	20
	Hepatocellular Cytoplasmic Vacuolation	0	0	2	13
	Average Severity:	0.0	0.0	0.2	1.1
<b>Day 211</b>					
Liver	Number Examined:	10	0	0	10
	Hepatocellular Cytoplasmic Vacuolation	1	-	-	3
	Average Severity:	0.1	-	-	0.3

**Text Table 19. Microscopic Liver Findings with Average Severity – Females**

<b>Tissue/Observation</b>	<b>Dose Group (mg/kg):</b>	<b>0</b>	<b>0.5</b>	<b>5</b>	<b>50</b>
<b>Day 92</b>					
Liver	Number Examined:	10	10	0	10
	Hepatocellular Cytoplasmic Vacuolation	0	0	-	0
	Average Severity:	0.0	0.0	-	0.0
<b>Day 183</b>					
Liver	Number Examined:	20	20	2	20
	Hepatocellular Cytoplasmic Vacuolation	0	0	0	0
	Average Severity:	0.0	0.0	0.0	0.0
<b>Day 211</b>					
Liver	Number Examined:	10	0	0	10
	Hepatocellular Cytoplasmic Vacuolation	0	-	-	0
	Average Severity:	0.0	-	-	0.0

## Toxicokinetics

Exposure (AUC and  $C_{max}$ ) to SAM (RDC-0313) increased greater than dose proportional over the 10-fold dosing range from 0.5 to 50 mg/kg/day for males and females. Females had significantly higher exposure levels than males at comparable doses, which can be explained by the significantly higher clearance rate and volume of distribution for males compared to females. There were no significant effects on the elimination half-life in males and females after repeated dosing. There was a small amount of drug accumulation, as measured by an increase in AUC, from day 1 to day 91, but not from day 91 to day 182. Plasma levels of metabolites RDC-9986 and RDC-1066 were not measured. A 14-day PK bridging study was conducted in rats (study no. AT-0313-41) using the same doses of SAM as those used in various pivotal toxicity studies, including 50 mg/kg/day, the high dose used in the 6-month repeat-dose study (see pharmacokinetics section of this review for details).

Blood samples for TK analysis were taken from TK satellite animals prior to and following dose administration on days 1, 91, and 182 at 0.25, 0.5, 1, 2, 4, 6, 12, and 24 hours after dosing.

**Table 2. TK Parameters for RDC-0313 on Day 1 Following Oral Administration of RDC-0313 to Rat [Mean; n=9/Sex; n=3/Scheduled Collection Time]<sup>a</sup>**

Gender	Dose (mg/kg)	Observed C <sub>max</sub> (ng/mL)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)
Male	0.5	1.45	1.00	ND <sup>b</sup>	ND <sup>b</sup>	ND <sup>b</sup>	ND <sup>b</sup>	1.20	ND <sup>b</sup>
	5	32.8	0.250	0.522	1.33	71,700	138,000	61.5	69.7
	50	1560	0.500	0.505	1.37	16,400	32,600	3040	3040
Female	0.5	39.3	1.00	0.395	1.76	5360	13,600	82.8	93.2
	5	366	0.500	0.320	2.17	3530	11,000	1380	1410
	50	6540	0.500	0.309	2.24	1560	5060	32,000	32,000

a. TK parameters were reported to three significant figures.

b. TK parameters not determined (ND) because Lambda Z could not be estimated.

**Table 3. TK Parameters for RDC-0313 on Day 91 Following Oral Administration of RDC-0313 to Rat [Mean; n=9/Sex; n=3/Scheduled Collection Time]<sup>a</sup>**

Gender	Dose (mg/kg)	Observed C <sub>max</sub> (ng/mL)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)
Male	0.5	4.03	0.250	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>	5.71	NR <sup>b</sup>
	5	44.1	1.00	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>	105	NR <sup>b</sup>
	50	2400	1.00	0.392	1.77	8670	22,100	5690	5760
Female	0.5	38.6	0.500	0.449	1.54	4770	10,600	97.3	105
	5	792	0.250	0.364	1.90	2570	7050	1920	1950
	50	10,000	2.00	0.211	3.29	980	4650	50,700	51,000

a. TK parameters were reported to three significant figures.

b. TK parameters not reported (NR) due to failure of acceptance criteria.

**Table 5. TK Parameters for RDC-0313 on Day 182 Following Oral Administration of RDC-0313 to Rat [Mean; n=9/Sex; n=3/Scheduled Collection Time]<sup>a</sup>**

Gender	Dose (mg/kg)	Observed C <sub>max</sub> (ng/mL)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)
Male	0.5	7.68	2.00	ND <sup>b</sup>	ND <sup>b</sup>	ND <sup>b</sup>	ND <sup>b</sup>	7.97	ND <sup>b</sup>
	5	75.5	1.00	0.426	1.63	28,900	67,900	159	173
	50	1650	1.00	0.172	4.04	10,100	58,900	4890	4940
Female	0.5	54.0	0.500	0.324	2.14	3020	9330	162	165
	5	659	0.250	0.345	2.01	2470	7180	1990	2020
	50	9360	0.500	0.256	2.71	1020	4000	48,800	48,900

a. TK parameters were reported to three significant figures.

b. TK parameters not determined (ND) because Lambda Z could not be estimated

## Dosing Solution Analysis

All dose formulations were within 8% of the target dose concentration and were stable.

### 6.2.2.1 Dog Sub-chronic

Sub-chronic repeat-dose toxicity studies in dogs include a 2-week oral toxicity study with a 2-week recovery period at initial doses 0, 2, 6 and 20 mg/kg/day, and a 13-week oral toxicity study with a 4-week recovery period at doses of 1, 3 and 10 mg/kg/day; all studies were adequate (studies AT-0313-08 and AT-0313-17, respectively). In the 2-week study, dosing was stopped after 3 doses to males and 2 doses to females due to excessive salivation that could not be distinguished from regurgitated dose and struggling with dosing. After a 39 to 40 day dosing holiday, the study was re-started using lower doses of 1, 3, and 10 mg/kg/day. Adverse emesis and excessive salivation occurred at 10 mg/kg/day, and there were slight decreases in mean body weight (6 to 7% compared to controls) and body weight gain, a decreased in food consumption at 10 mg/kg/day in males and all doses in females. Lower thymus weights were observed at 10 mg/kg/day in females, however there were no correlating microscopic findings and therefore the effect was not considered toxicologically relevant. The NOAEL was 3 mg/kg/day due to increased emesis at 10 mg/kg/day. Similar to the rat, SAM decreased body weight that correlated with decreased food intake. In the 13-week study, body weight gain was 80% that of the controls for males and females with a corresponding decrease in food consumption observed in high dose males with partial recovery. There was a non-dose-dependent decrease in body weight for females at all doses and only a slight decrease in food consumption at the high dose. Thymus weights were decreased in high dose males with histopathological finding of atrophy, which was partially reversible. Thymic atrophy is a common finding in dogs and is not considered toxicologically relevant. Spleen weights were decreased in high dose females as well as adrenal gland vacuolation was observed in high dose females. Similarly, the toxicological relevance of the spleen and adrenal changes in females is unknown. The decrease in food consumption and resulting decrease in body weight observed in male rats and dogs is most likely due to the pharmacology of opioid antagonists which are known to reduce palatable food intake in animals. The NOAEL in the 13-week dog study is 3 mg/kg/day for males and females due to a significant decrease in body weight gain at 10 mg/kg/day.

### 6.2.2.2 Dog 9-month

**Study title:** 39-week oral gavage toxicity study of RDC-0313 in beagle dogs with a 4-week recovery period

Study no.:	AT-0313-19
Study report location:	SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 11, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RDC-0313-02, lot # CMLW-225/09-AR4, 97.1%

## Key Study Findings

- Drug related clinical signs in both sexes at 3 and 10 mg/kg/day included transient head shaking, excessive salivation, and lip smacking which appear to be duration related as they were not seen at higher doses in the 13-week study above and not observed during the recovery period.
- Dose-related and statistically significant decrease in mean body weight in males and females at 3 and 10 mg/kg/day (>10% compared to controls), partially reversible and did not correlate to change in food intake.
- Exposure to parent increased greater than dose-proportional and there was modest accumulation after repeated dosing. Exposure to metabolite RDC-9986 increased roughly dose-proportional.
- NOAEL = 1 mg/kg/day in males and females based on >10% decrease in mean body weight at higher doses.
- Safety margins at the NOAEL are approximately 1 times compared to exposure at the MRHD of 10 mg SAM based on AUC at steady state on day 273 for males and females.

## Methods

Doses:	0, 1, 3, 10 mg/kg/day
Frequency of dosing:	Once daily for 273 days
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	Solution/sterile water
Species/Strain:	Dog/Beagle from [REDACTED] (b) (4)
Number/Sex/Group:	6/sex/control and high dose groups, 4/sex/low and mid dose groups
Age:	At dosing initiation: 6 to 8 months
Weight:	At dosing initiation: 8.7 to 13.8 kg
Satellite groups:	4-week recovery period: 2/sex/control and high dose groups
Unique study design:	NA
Deviation from study protocol:	None that affected study integrity.

## Observations and Results

### Mortality

None

### Clinical Signs

Drug-related clinical signs of excessive salivation, head shaking, and lip smacking were observed throughout the study approximately 30 minutes after dosing in 1 to 2 animals at 3 mg/kg/day and all animals at 10 mg/kg/day. The findings generally resolved within 1 to 2 hours after dosing. These findings were not considered adverse but are drug-

related and could be duration related as they were not observed in the 13-week study at higher doses; also, these findings were not observed during the recovery period. Other clinical signs observed sporadically in some animals included diarrhea, emesis, mucoid feces, reduced/absent feces, soft feces, reddened ear and discharge, abrasion, limping, swelling of foot/head, and vaginal discharge. These findings did not occur in a dose-related manner and therefore were considered incidental and not drug-related. One high dose female had convulsions on three occasions (days 148, 151, and 267). Since the occurrence of seizures was only observed on a few days and only in one animal, and seizures can occur sporadically in dogs, the finding is most likely incidental. Cage-side observations were performed twice daily during the dosing phase, once prior to dosing and 1 to 2 hours after dosing. Cage-side observations were recorded at least once during the recovery phase.

**Table 5. Summary of Clinical Abnormalities, Post-Dosing Observations – Males**

Group	Observation	Observed			Total Number
		Animals Affected	First Day	Last Day	
3 – 3 mg/kg	Excessive Salivation	2	176	233	3
4 – 10 mg/kg	Excessive Salivation	6	2	260	70
3 – 3 mg/kg	Head Shaking	1	120	120	1
4 – 10 mg/kg	Head Shaking	6	3	260	53
4 – 10 mg/kg	Lip Smacking	6	1	260	41

**Table 6. Summary of Clinical Abnormalities, Post-Dosing Observations – Females**

Group	Observation	Observed			Total Number
		Animals Affected	First Day	Last Day	
2 – 1 mg/kg	Excessive Salivation	1	203	203	1
3 – 3 mg/kg	Excessive Salivation	2	175	259	4
4 – 10 mg/kg	Excessive Salivation	6	2	259	64
3 – 3 mg/kg	Head Shaking	1	175	175	1
4 – 10 mg/kg	Head Shaking	5	2	259	39
3 – 3 mg/kg	Lip Smacking	2	119	175	2
4 – 10 mg/kg	Lip Smacking	6	2	232	27

[Total number: the total number of occurrences for the observation amongst all animals affected with the finding.]

## Body Weights

There was a dose-related and statistically significant decrease in group mean body weight for males and females compared to controls. At the end of the dosing period on day 274 there was a 6, 12, and 14% decrease in mean body weight for males and a 7, 11, and 13% decrease in mean body weight for females at 1, 3, and 10 mg/kg/day compared to controls. Body weight gain values were also dose-dependently decreased. The effect on body weight did not correspond directly to effect on food consumption. The Applicant did not consider the decrease in body weight to be adverse; however, this reviewer considers it to be adverse at 3 and 10 mg/kg/day in both sexes because the magnitude of the effect was greater than a 10% decrease compared to controls. Mean body weights were increased at 10 mg/kg/day for males and females at the end of the recovery period compared to the last day of dosing, indicating partial recovery. Body

weights were recorded prior to group assignment, on study day 1 prior to dosing, and weekly thereafter, and on the day of necropsy.

### **Food Consumption**

There were several instances of statistically significant changes in food consumption in drug-treated groups compared to controls, however the changes occurred sporadically and not in a dose-related manner, therefore the effects were not considered drug-related. Food consumption was measured daily.

### **Ophthalmoscopy**

There were no drug-related findings. Eye exams were conducted prior to group assignment and during weeks 20 and 39.

### **ECG**

There were no drug-related findings on any of the cardiovascular parameters measured, including no abnormal ECG findings. ECGs were recorded on all animals prior to group assignment and during weeks 20 and 39 at 1 to 2 hours post-dose. QTc intervals were calculated according to the method of Fridericia's formula. A qualitative evaluation of all ECG tracings was made by a veterinary cardiologist, and a separate narrative was included in the study report.

### **Hematology**

There were no adverse drug related effects. The following were small, not dose-related and/or within historical range. Small but statistically significant increases in red blood cell counts, hemoglobin, and hematocrit for males at 1 and 3 mg/kg/day, compared to controls, and increase in activated partial thromboplastin time and prothrombin time for females at 10 mg/kg/day (6 to 10% compared to controls). Hematology, coagulation, serum chemistry, and urinalysis assessments were performed on all fasted animals prior to group assignment, during week 20, and on day 274 prior to necropsy. Hematology and serum chemistry was also assessed during the recovery period on day 302 prior to necropsy. Adequate parameters were evaluated.

### **Clinical Chemistry**

There were no adverse drug related effects. The following were small, not dose-related and/or within historical range. Slight increases in albumin/globulin ratio in all drug-treated male groups compared to controls and increased glucose levels in high dose females compared to controls.

### **Urinalysis**

There were no clear drug-related findings.

### **Gross Pathology**

There were no drug-related macroscopic findings.

### **Organ Weights**

There were no drug-related effects on organ weights.

### **Histopathology**

Adequate Battery: Yes

Peer Review: Yes

### Histological Findings

The only potentially drug related effect is minimal and mild chronic inflammation of the exocrine pancreas observed in one high dose male and one high dose female. The inflammation was described as focal in distribution and not consistent with drug-induced pancreatic lesions, as noted by the reviewing pathologist. However, pancreatic effects including microscopic findings of eosinophilic cytoplasmic vacuoles in endocrine islet cells were observed in male rats in the 13-week study at the high dose of 250 mg/kg/day, therefore the pancreatic finding in dogs cannot be ruled out as being possibly drug-related. Necrotizing inflammation of small arteries was observed in the epididymis of one high dose male, but the finding was considered to be attributed to Idiopathic Juvenile Arteritis and not drug-related by the reviewing pathologist. Without any additional findings in other drug-treated males, this finding is likely incidental and not drug-related.

### Toxicokinetics

Plasma exposure to parent drug increased greater than dose proportional over the dose range of 1 to 10 mg/kg/day for males and females on day 1 and day 273. The elimination half-life increased slightly with increasing dose in males and females, while the apparent clearance decreased with increasing dose. Exposure (AUC) to parent drug increased after repeated dosing in males and females at all dose levels, indicating drug accumulation over time. Exposure to metabolite RDC-9986 increased in a dose-proportional manner in males and females. The elimination half-life of the metabolite was greater (2.3 to 6.0-fold) than that of parent drug. There were no major sex differences in exposure to either parent or metabolite.

#### Day 1:

Group		Observed	Observed	Terminal	Apparent	AUC <sub>last</sub>	AUC <sub>∞</sub>
		C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	Elimination Half-Life (hr)	Clearance (mL/hr/kg)	(hr*ng /mL)	(hr*ng /mL)
<b>Male</b>							
2 – 1 mg/kg	Mean	75.5	2.00 <sup>a</sup>	1.79	3090	338	342
	SE	17.6	0.00	0.12	550	53	53
3 – 3 mg/kg	Mean	469	0.250 <sup>a</sup>	2.32	1670	1990	2010
	SE	66	0.583	0.53	370	490	490
4 – 10 mg/kg	Mean	818	1.00 <sup>a</sup>	2.86	1860	5680	5710
	SE	33	1.67	0.22	340	950	960
<b>Female</b>							
2 – 1 mg/kg	Mean	108	1.00 <sup>a</sup>	1.64	2520	395	398
	SE	10	0.33	0.04	90	14	13
3 – 3 mg/kg	Mean	408	1.00 <sup>a</sup>	1.86	1990	1510	1530
	SE	21	0.25	0.14	170	130	140
4 – 10 mg/kg	Mean	1580	1.00 <sup>a</sup>	2.70	1390	7400	7420
	SE	340	0.25	0.24	180	910	900

TK parameters were reported to three significant figures.

a. Represents the median.

**Day 273:**

Group		Observed C <sub>max</sub> (ng/mL)	Observed T <sub>max</sub> (hr)	Terminal	Apparent Clearance (mL/hr/kg)	AUC <sub>last</sub> (hr*ng /mL)	AUC <sub>∞</sub> (hr*ng /mL)
				Elimination Half-Life (hr)			
<b>Male</b>							
2 – 1 mg/kg	Mean	129	1.00 <sup>a</sup>	1.92	2360	442	457
	SE	19	0.51	0.22	440	88	88
3 – 3 mg/kg	Mean	690	1.00 <sup>a</sup>	3.10	761	3980	4000
	SE	59	0.00	0.15	65	340	340
4 – 10 mg/kg	Mean	2460	1.00 <sup>a</sup>	3.49	764	13,800	13,900
	SE	220	0.25	0.36	129	2400	2500
<b>Female</b>							
2 – 1 mg/kg	Mean	113	2.00 <sup>a</sup>	1.66	2020	494	499
	SE	6	0.00	0.01	110	26	26
3 – 3 mg/kg	Mean	557	1.00 <sup>a</sup>	3.02	1190	2570	2580
	SE	18	0.51	0.15	120	280	280
4 – 10 mg/kg	Mean	2200	1.00 <sup>a</sup>	2.91	952	10,700	10,800
	SE	210	0.25	0.17	105	1100	1100

TK parameters were reported to three significant figures.

a. Represents the median.

**Dosing Solution Analysis**

All dose formulations were within 4% of the target drug concentration, and within acceptable limits.

**6.2.3 OLZ+SAM 13-week combination study**

**Study title:** RDC-0313 and olanzapine: 13-week oral toxicity study in dogs with a 4-week recovery period

Study no.:	AT-0313-34
Study report location:	SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 9, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RDC-0313-02 (malate salt), lot no. 1145L030, 99.7% Olanzapine, batch no. OL11011037 from (b) (4) 99.8%

**Key Study Findings**

- No new toxicities were identified when OLZ and SAM (RDC-0313) were co-administered compared to toxicities identified with OLZ and SAM alone.

- CNS-related clinical signs including tremors and ataxia, and GI-related signs including emesis and feces changes were observed in males and females after treatment with OLZ, SAM, and the combination.
- Reversible organ weight changes with accompanying microscopic findings were observed in male and female reproductive tract organs (epididymides, prostate, and mammary gland) and were attributed to olanzapine treatment. Non-adverse, partially reversible decreases in thymus weights with corresponding microscopic findings of lymphoid depletion were observed in males only after treatment with OLZ, SAM, and the combination.
- NOAEL = 5/10 mg/kg/day OLZ/SAM  
 AUC values on day 91: Males: 12600; 10100; 2250 ng.hr/ml for RDC-0313, RDC-9986, OLZ  
 Females: 9140; 14400; 2140 ng.hr/ml for RDC-0313, RDC-9986, OLZ

## Methods

Doses:	RDC-0313: 0, 10, 3, 10 mg/kg/day Olanzapine: 0, 5, 1.5, 5 mg/kg/day (see Sponsor's dosing table below)
Frequency of dosing:	Once daily for 91 days
Route of administration:	Oral gavage for RDC-0313 and oral capsules for olanzapine
Dose volume:	For RDC-0313: 5 ml/kg
Formulation/Vehicle:	RDC-0313: sterile water for injection (10 ml for control) Olanzapine: size 12 gelatin capsules for olanzapine control: empty size 12 gelatin capsule
Species/Strain:	Dog/Beagle from <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>
Number/Sex/Group:	3/sex/group
Age:	10 months at time of receipt
Weight:	At randomization: males: 7.75-14.65 kg; females: 7.15-9.95 kg
Satellite groups:	2/sex/groups 1-3 and 5 for 4-week recovery
Unique study design:	4-week recovery group was included
Deviation from study protocol:	Few minor deviations but none that affected the outcome of the study results.

Sponsor's dosing table:

<b>Administration Details</b>				
<b>Group</b>	<b>Encapsulated Olanzapine (mg/kg/day)</b>	<b>Oral Gavage Sterile Water for Injection (mL)</b>	<b>Oral Gavage RDC-0313 (mg/kg/day)<sup>a</sup></b>	<b>RDC-0313 Concentration (mg/mL)</b>
1	0 (empty capsule)	10	NA	NA
2	5	10	NA	NA
3	0 (empty capsule)	NA	10	2
4	1.5	NA	3	0.6
5	5	NA	10	2

<sup>a</sup>RDC-0313-02 was administered at a dose volume of 5 mL/kg/dose.  
NA – Not applicable

### **Dose Selection**

A dose range-finding study (no. AT-0313-33: RDC-0313 and olanzapine: a 21-day oral dose range-finding toxicity study in dogs) was conducted to aid in dose selection for the pivotal combination study. 2 dogs/sex/group were administered 0 (empty capsule and fixed volume of 10 ml/animal sterile water), 10/0, 5/10, and 10/10 olanzapine/RDC-0313 mg/kg/day. Blood samples were collected from all animals on days 1 and 21 for determination of the plasma concentrations and toxicokinetics of RDC-0313, RDC-9986, olanzapine, and N-desmethyl olanzapine. There was no RDC-0313 alone group. One male at 10/10 mg/kg/day olanzapine/RDC-0313 was euthanized moribund on day 7 due to marked body weight loss (25% of its pretest body weight), inappetence, moderate reduction in sodium and chloride, mild increases in total protein, albumin and globulin, erythrocyte mass. There was no macro- or microscopic findings to determine a cause of death. Body weight loss and decreased food consumption was observed in other animals from that same dose group. CNS-related clinical signs including decreased activity and ataxia were observed in all animals on day 1. Findings consistent with an inflammatory response (increased neutrophils, monocytes, leukocytes) were observed in males and females at 10/10 olanzapine/RDC-0313. At 10/10 mg/kg/day olanzapine/RDC-0313, thymus weights were decreased, and liver weights were increased and corresponding lymphoid depletion in the thymus and minimal centrilobular vacuolation in the liver were observed in these animals. 10/10 mg/kg/day olanzapine/RDC-0313 was considered to be greater than an MTD in this study.

### **Observations and Results**

#### **Mortality**

None

#### **Clinical Signs**

Daily Dose (mg/kg/day) <sup>b</sup>	0/0		5/0		0/10		1.5/3		5/10	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 3	F: 3	M: 5	F: 5
<b>Noteworthy Findings:</b>										
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	0	0
Body Weight	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
<b>Clinical Observations<sup>d</sup></b>										
Activity decreased	1/1	0/0	52/5	37/5	1/1	0/0	4/2	4/3	30/5	12/4
Ataxia	0/0	0/0	6/4	10/4	0/0	0/0	1/1	0/0	3/2	1/1
Eyelid partially/completely closed	0/0	0/0	2/1	6/3	0/0	0/0	0/0	0/0	4/2	3/2
Feces few/absent	0/0	0/0	0/0	0/0	0/0	0/0	2/1	0/0	2/1	1/1
Feces mucoid	0/0	0/0	2/1	0/0	2/2	13/4	0/0	0/0	2/1	0/0
Feces soft	42/5	15/5	143/5	70/5	105/5	77/5	110/3	35/3	185/5	114/5
Feces watery	2/1	2/2	65/4	19/3	21/2	4/3	49/3	14/2	99/5	33/4
Mammary enlargement	0/0	1/1	0/0	13/2	0/0	0/0	0/0	21/3	0/0	37/3
Nictitating membrane protruding	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	10/3	2/1
Posture hunched	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	6/1
Struggling during dosing	0/0	0/0	0/0	0/0	8/3	3/1	0/0	0/0	16/4	1/1
Tremors	0/0	0/0	4/4	4/3	1/1	2/2	0/0	1/1	1/1	5/4
Vomitus, Tan	0/0	6/1	0/0	1/1	4/3	5/3	4/1	1/1	14/4	9/4
Vomitus, Unable to readminister	0/0	3/1	1/1	1/1	1/1	1/1	0/0	0/0	2/1	0/0
Vomitus, White	0/0	1/1	1/1	0/0	2/2	7/5	2/2	1/1	4/1	0/0
Vomitus, Yellow	0/0	1/1	0/0	1/1	0/0	3/3	0/0	0/0	1/1	0/0

<sup>b</sup> Olanzapine/RDC-0313. Group 1 control animals received an empty capsule and a fixed volume of SWI (10 mL); Group 2 animals received an olanzapine capsule (5 mg/kg) and a fixed volume of SWI (10 mL); and Group 3 animals received an empty capsule and RDC-0313 (10 mg/kg).

<sup>d</sup> Weeks 1 to 13. Presented as total number of times observed/total number of animals affected.

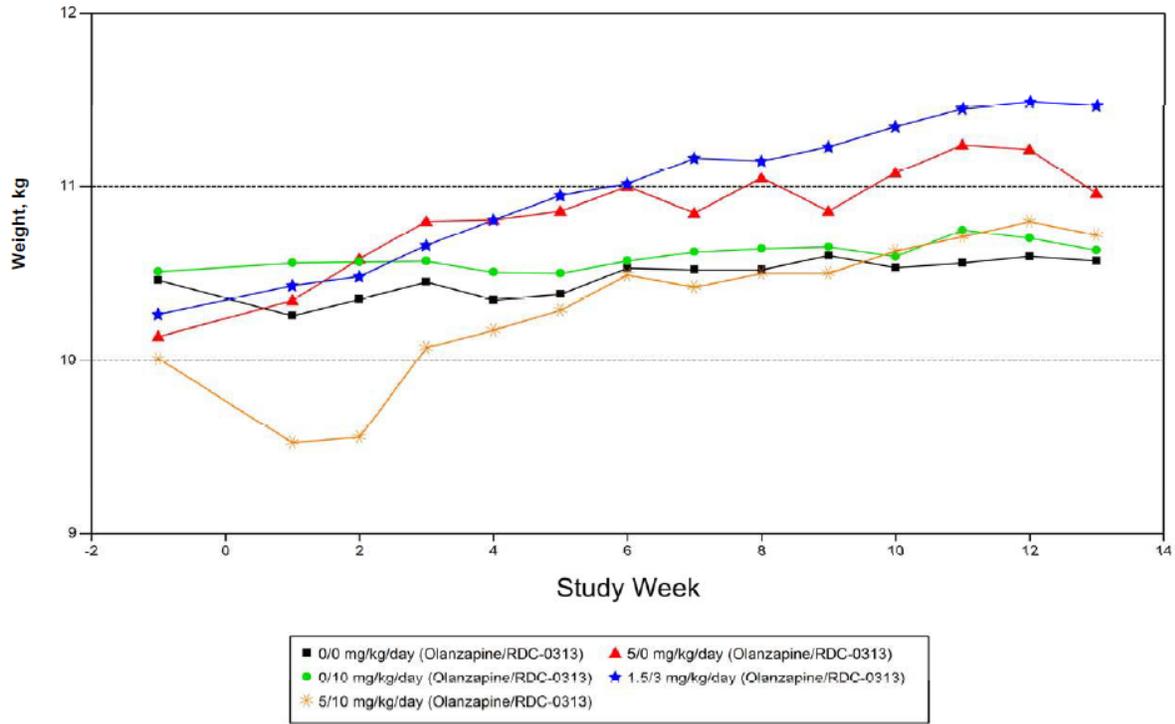
[Source: NDA 213378, Toxicology tabulated summary]

Very few new clinical signs were observed in animals administered the combination of olanzapine + RDC-0313 compared to those signs observed in animals administered either drug alone. New signs included hunched posture in 1 female at 5/10 mg/kg/day and protruding nictitating membrane (which is not clinically relevant) in 3 males and 1 female at 5/10 mg/kg/day, which occurred during the first 2 weeks of dosing. Other drug-related clinical signs observed in animals treated with olanzapine or RDC-0313 either alone or in combination included tremors, increased incidence of decreased activity, soft/watery feces (which was also observed in controls, but at a higher frequency in drug-treated groups), emesis, tremors and ataxia (in olanzapine treated groups during the first week of study). Struggling during dosing was only observed in animals administered 10 mg/kg/day RDC-0313. Mammary gland enlargement appeared to be related to olanzapine, as it was not observed in the RDC-0313 alone group but was observed in all female groups administered olanzapine either alone or in combination. Cageside observations were conducted twice daily, and detailed clinical examinations were conducted once per week (no mention of what time after dosing the exams were conducted).

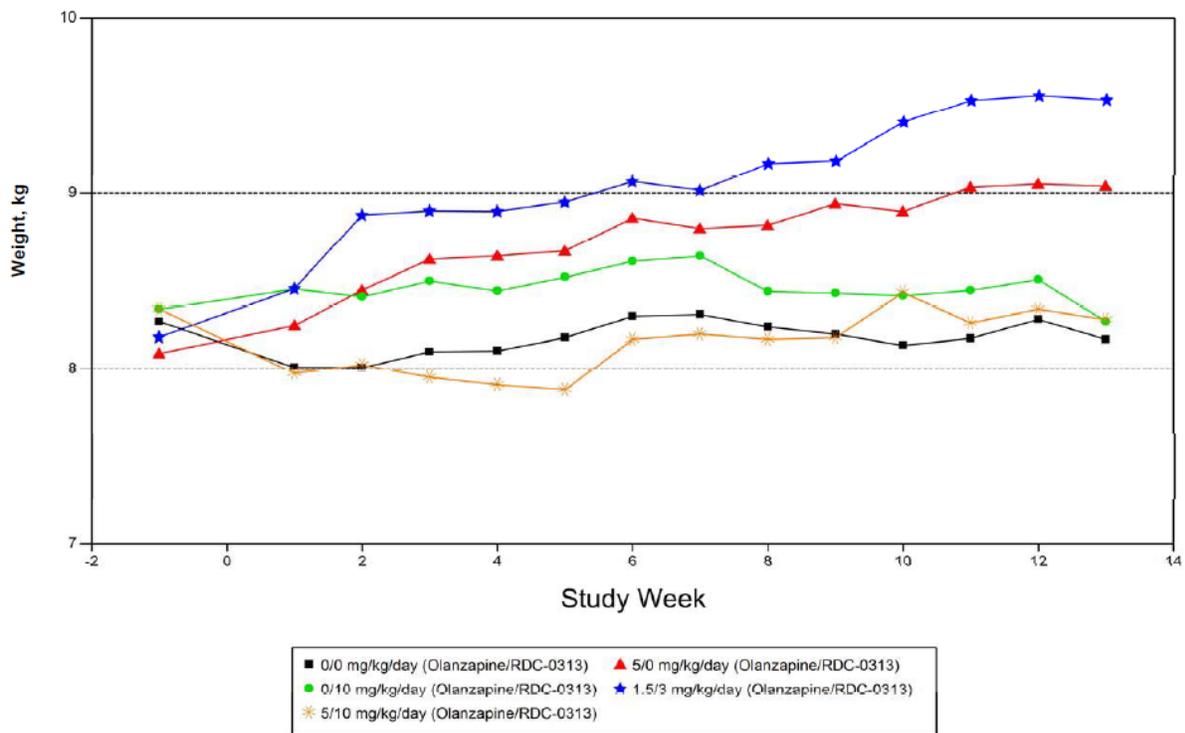
## Body Weights

There was a transient decrease in body weight for males at 5/10 mg/kg/day during the first two weeks of dosing compared to controls. However, the effect did not reach statistical significance and resolved by week 4. There was a trend for an increase in body weight gain in the 1.5/3 mg/kg/day and olanzapine-alone male and female groups compared to controls, but the changes did not reach statistical significance. The effects on body weight correlated with effects on food consumption. Body weights were recorded within 3 days of animal receipt, once prior to randomization, and weekly during the study period.

### Mean Body Weight Values - MALE



### Mean Body Weight Values - FEMALE



### **Food Consumption**

Only a few isolated instances of statistically significant changes in food consumption were observed in various dose groups compared to controls, including decreases in food consumption for males at 5/10 mg/kg/day. Food consumption was recorded daily during the study period.

### **Ophthalmoscopy**

There were no drug-related findings. Eye exams were conducted by a veterinary ophthalmologist once pretest and once prior to terminal and recovery necropsies.

### **ECG**

All animals were in sinus rhythm or sinus arrhythmia, which are normal rhythms in dogs. One female at 0/10 mg/kg/day olanzapine/RDC-0313 had 3 ventricular escape beats at the predose ECG and 2 at the post dose ECG conducted at the end of the study. These are considered a normal response, were only observed in one animal and the number did not increase after dosing, therefore were not considered drug-related. Overall, there was no drug-related effect on any ECG parameters (qualitative or quantitative). ECGs (10 lead) were recorded prior to initiation of dosing and again predose and 1-2 hours postdose during the last week of dosing, and during the last week of the recovery period. A consultant veterinary cardiologist interpreted the ECGs and a report is included the electrocardiography report (QA). QTc was calculated using Fridericia's correction.

### **Hematology**

There were no clear overall drug-related effects on any hematology or coagulation parameters for olanzapine, RDC-0313 or the combination of both. All changes were considered within acceptable ranges for biologic variation or procedure-related. One male at 5/0 mg/kg/day olanzapine/RDC-0313 did have moderate increases in total leukocytes, neutrophils, and monocytes with decreases in lymphocytes and eosinophils, which are consistent with inflammation and/or stress; however, since it only occurred in one animal it may be incidental or related to stress. It should be noted that a few animals in the dose range-finding study were also observed to have a similar inflammatory type response at a dose of 10/10 mg/kg/day olanzapine/RDC-0313. Blood samples were collected from all animals (overnight fasted) during pretest and prior to terminal and recovery necropsies. An adequate battery of hematology and coagulation parameters was evaluated.

### **Clinical Chemistry**

Creatinine levels for males at 5/0 and 5/10 mg/kg/day were slightly, but statistically significantly, decreased compared to controls at the terminal necropsy, 19% and 16% compared to controls, respectively. Values were similar to control levels at the end of the recovery period. Blood samples were collected from all animals (overnight fasted) during pretest and prior to terminal and recovery necropsies. An adequate battery of clinical chemistry parameters was evaluated.

### **Urinalysis**

Urine volume was increased for males and females at all dose levels, but the greatest increase was observed at 1.5/3 mg/kg/day, over 300% compared to controls for both males and females. The effect was not dose-dependent. Although there was no recovery group for the 1.5/3 mg/kg/day olanzapine/RDC-0313 dose, there was no relevant effect on urine volume observed in all other recovery groups. Specific gravity was also significantly decreased for females only at 1.5/3 and 5/10 mg/kg/day olanzapine/RDC-0313, ~2% compared to controls. Specific gravity levels were comparable to controls for all recovery groups. There were no correlative kidney findings in any group. Urine samples were collected using steel pans placed under cages for a total time of 16 hours during pretest and prior to terminal and recovery necropsies. An adequate battery of urinalysis parameters, including microscopic examination of sediment, was evaluated.

### **Gross Pathology**

At the terminal necropsy, one female at 5/0 mg/kg/day olanzapine/RDC-0313 had a swollen/thickened mammary gland and a subcutaneous mass which correlated with lobular gland hyperplasia and hyperplasia atypia found microscopically. These findings were attributed to olanzapine treatment.

### **Organ Weights**

Drug-related effects on organ weights were observed for thymus (males only), epididymides, and prostate. There was a decrease in absolute and relative thymus weights observed in males mainly at 5/10 mg/kg/day and to a lesser extent at 5/0 mg/kg/day olanzapine/RDC-0313. The addition of RDC-0313 resulted in a greater decrease in thymus weights, however there was no effect on thymus weights in animals administered RDC-0313 alone, therefore the effect is most likely due to olanzapine treatment. The decrease in thymus weights in the olanzapine treated males corresponded microscopically with cortical lymphoid depletion. There were no effects (or a slight increase compared to controls, but there were only 2 animals/group) on thymus weights observed in any recovery group animals, indicating full reversibility. There was a decrease in epididymide and prostate weights in all groups treated with the olanzapine (5/0, 1.5/3 and 5/10 mg/kg/day olanzapine/RDC-0313), and not in the RDC-0313 alone group indicating these effects were solely due to olanzapine. The addition of RDC-0313 also did not exacerbate the effects. The decrease in epididymide and prostate weights correlated microscopically with mineralization in the epididymides and atrophy of the prostate. In the recovery group animals, there was still a slight decrease in epididymide weights (relative to body weight) at 5/0 and 5/10 mg/kg/day compared to controls and in prostate weights at 5/0 mg/kg/day indicating some recovery but not complete.

Test Article-related Organ Weight Changes - Terminal Male (Percent change relative to control)				
Dose level: mg/kg/day*	5/0	0/10	1.5/3	5/10
Sex	M	M	M	M
Number Examined	3	3	3	3
Thymus (g)	↓25.48	↓12.86	↑32.88	↓29.70
Thymus/BWt%	↓8.83	↑1.23	↑14.72	↓21.96
Thymus/BrWt ratio	↓17.02	↓2.00	↑29.39	↓28.12
BWt - Body Weight	↑ - Increased			
BrWt - Brain Weight	↓ - Decreased			
M - Male	*Olanzapine/RDC-0313			

Test Article-related Organ Weight Changes - Terminal Male (Percent change relative to control)				
Dose level: mg/kg/day*	5/0	0/10	1.5/3	5/10
Sex	M	M	M	M
Number Examined	3	3	3	3
Epididymides (g)	↓32.35	↓16.90	↓17.05	↓32.07
Epididymides/BWt%	↓20.97	↓4.84	↓21.24	↓26.08
Epididymides/BrWt ratio	↓25.46	↓6.78	↓14.58	↓31.21
Prostate (g)	↓66.17 <sup>a</sup>	↓3.02	↓27.68	↓67.09 <sup>a</sup>
Prostate/BWt%	↓60.03 <sup>a</sup>	↑15.74	↓24.62	↓63.32 <sup>a</sup>
Prostate/BrWt ratio	↓62.61 <sup>a</sup>	↑9.25	↓23.70	↓66.57 <sup>a</sup>
<sup>a</sup> Significantly different from control; (p<0.05)	↑ - Increased			
BWt - Body Weight	↓ - Decreased			
BrWt - Brain Weight	M - Male			
	*Olanzapine/RDC-0313			

Test Article-related Organ Weight Changes - Recovery Male (Percent change relative to control)			
Dose level: mg/kg/day*	5/0	0/10	5/10
Sex	M	M	M
Number Examined	2	2	2
Epididymides (g)	↓7.04	↓0.47	↓8.75
Epididymides/BWt%	↓27.71	↓18.64	↓22.17
Epididymides/BrWt ratio	↑5.34	↓9.62	↑6.41
Prostate (g)	↓38.07	↓16.63	↓10.26
Prostate/BWt%	↓51.36	↓34.37	↓22.95
Prostate/BrWt ratio	↓29.66	↓25.32	↑5.40
BWt - Body Weight	↑ - Increased		
BrWt - Brain Weight	↓ - Decreased		
M - Male	*Olanzapine/RDC-0313		

There were several other changes in organ weights (absolute and/or relative to body and/or brain weight) when compared to controls, but the effects were considered normal background variation and not drug-related by the Sponsor because the effects were small in magnitude, not dose-dependent and there were no corresponding microscopic findings.

### **Histopathology**

Adequate Battery: Yes. Tissues from all animals were examined microscopically. Only target organ tissues (epididymides, thymus, prostate, ovaries, uterus with cervix, vagina and mammary gland), gross lesions and any tissue masses with regional lymph nodes were examined from the recovery group animals. 4 sections of brain (cerebrum, midbrain, cerebellum, medulla/pons).

Peer Review: Yes

### Histological Findings

Lymphoid depletion in the thymus was observed in almost all animals, males and females, from all dose groups indicating an effect by both olanzapine and RDC-0313. However, the severity increased mild to severe in the 5/0, 0/10 and 5/10 mg/kg/day groups compared to a severity of only minimal to mild in the controls and 1.5/3 mg/kg/day groups. There appeared to be full recovery of this effect as the incidence and severity level was equal across all dose groups, including controls, with no incidence of a severe finding in any recovery group animals. The effects observed in the thymus may not be drug-related but rather secondary to stress as the findings also occurred in control animals. Other microscopic findings were observed in male and female reproductive organs including, prostate, epididymides, mammary glands, ovaries and uterus and were all attributed to olanzapine treatment only. Atrophy of the prostate (minimal to moderate) was observed in all males at 5/0 and 5/10 mg/kg/day, and 1/3 males at 1.5/3 mg/kg/day olanzapine/RDC-0313 with no incidence in the RDC-0313 alone treated group. The atrophy was characterized by a shrunken gland that contained flattened low cuboidal basophilic epithelium with no glandular secretion and increased amount of connective tissue. Only 1 of the 2 recovery group males at 5/10 mg/kg/day olanzapine/RDC-0313 had minimal atrophy of the prostate indicating reversibility. All 3 males at 5/0 mg/kg/day olanzapine/RDC-0313 had mineralization of the epithelium of the epididymis (head section) compared to none or 1 male in all other groups. There was no observation of this effect in any recovery group animals, indicating the effect was reversible. Hyperplasia with atypia, characterized by ductal enlargement and dilation with fibrosis and proliferation of spindle-shaped basophilic epithelial cells that formed small clumps with the lumen, was observed in the mammary gland of 1 female each at 5/0 and 5/10 mg/kg/day olanzapine/RDC-0313 and was considered related to olanzapine. Minimal lobular hyperplasia (increased number of glands) was observed in all drug-treated female groups (1, 1, 2, and 1 at 5/0, 0/10, 1.5/3 and 5/10 mg/kg/day olanzapine/RDC-0313. All mammary glands observed at the end of the recovery period were within normal limits. It was not clear from the Sponsor if the effects observed in the mammary glands were drug-related or related to normal estrus cycle morphology; however, olanzapine and other antipsychotics that act on dopamine receptors cause mammary gland hyperplasia in animals due to increased prolactin (the latter was not

measured in this study). Two females each at 5/0 and 5/10 mg/kg/day olanzapine/RDC-0313 also had mild atrophy of the ovaries and uterus, characterized by absence of corpora lutea and reduction in size and number of secondary follicles in the ovaries and reduction in size. All findings at the end of the recovery period were consistent with normal estrus cycle. This finding is attributed to olanzapine treatment. All of these effects are extension of olanzapine pharmacology.

Test Article-related Microscopic Observations - Terminal										
Dose level: mg/kg/day*	0/0		5/0		0/10		1.5/3		5/10	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	3	3	3	3	3	3	3	3	3	3
<b>Thymus</b>										
Depletion, lymphoid, cortex	3	3	3	2	3	3	2	3	3	2
-minimal	1	0	0	0	0	0	1	1	0	0
-mild	2	3	0	0	1	2	1	2	1	0
-moderate	0	0	1	1	2	1	0	0	1	1
-severe	0	0	2	1	0	0	0	0	1	1
M - Male F - Female *Olanzapine/RDC-0313										

Test Article-related Microscopic Observations - Recovery									
Dose level: mg/kg/day*	0/0		5/0		0/10		5/10		
Sex	M	F	M	F	M	F	M	F	
Number Examined	2	2	2	2	2	2	2	2	
<b>Thymus</b>									
Depletion, lymphoid, cortex	2	2	2	2	2	2	2	2	
-minimal	0	1	0	1	1	1	1	0	
-mild	1	1	2	1	1	0	1	2	
-moderate	1	0	0	0	0	1	0	0	
M - Male F - Female *Olanzapine/RDC-0313									

## Toxicokinetics

Blood samples for TK analysis were taken from all animals on days 1 and 91 prior to dosing and at 0.25, 1, 2, 6, 12, and 24 hours after dosing. TK analysis was conducted for RDC-0313, RDC-9986, and olanzapine. There were no sex differences in exposure for RDC-0313, RDC-9986 or olanzapine. There was no evidence of drug accumulation from day 1 to 91 for RDC-0313 or RDC-9986, however exposure levels (AUC) for olanzapine increased about 2-fold from day 1 to 91. The addition of olanzapine did not have any effect on exposure or TK parameters of RDC-0313, including  $T_{max}$  and  $T_{1/2}$ , when RDC-313 was administered alone.

Mean Toxicokinetic Parameters for RDC-0313 in Dogs Administered Daily Oral Doses of Olanzapine and RDC-0313 <sup>a</sup> for 91 Days					
Sex	Olanzapine Dose (mg/kg/day)	RDC-0313 Dose (mg/kg/day)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>(0-24)</sub> (ng*hr/mL)
Day 1					
Male	0	10	1360	1.00	10,300
	1.5	3	470	1.33	1870
	5	10	1570	1.40	10,700
Female	0	10	1360	1.85	9140
	1.5	3	510	1.33	2470
	5	10	991	1.20	6910
Day 91					
Male	0	10	1810	0.700	11,000
	1.5	3	522	1.00	2450
	5	10	1320	1.40	12,600
Female	0	10	1870	1.05	10,200
	1.5	3	549	1.08	3010
	5	10	1620	1.20	9140
<sup>a</sup> Administered as the malic acid salt (RDC-0313-02) of the active moiety. AUC <sub>(0-24)</sub> = Area under the plasma concentration-time curve from time zero to 24 hours postdose.					

<b>Mean Toxicokinetic Parameters for RDC-9986 in Dogs Administered Daily Oral Doses of Olanzapine and RDC-0313<sup>a</sup> for 91 Days</b>					
Sex	Olanzapine Dose (mg/kg/day)	RDC-0313 Dose (mg/kg/day)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>(0-24)</sub> (ng*hr /mL)
Day 1					
Male	0	10	838	3.20	11,400
	1.5	3	407	1.33	3370
	5	10	801	1.80	10,200
Female	0	10	1050	4.20	12,600
	1.5	3	370	3.33	4090
	5	10	859	2.60	12,800
Day 91					
Male	0	10	950	2.00	11,400
	1.5	3	362	1.00	3620
	5	10	667	4.40	10,100
Female	0	10	1090	2.60	13,400
	1.5	3	343	3.33	4290
	5	10	1160	2.40	14,400
<sup>a</sup> Administered as the malic acid salt (RDC-0313-02) of the active moiety. AUC <sub>(0-24)</sub> = Area under the plasma concentration-time curve from time zero to 24 hours postdose.					

Mean Toxicokinetic Parameters for Olanzapine in Dogs Administered Daily Oral Doses of Olanzapine and RDC-0313 <sup>a</sup> for 91 Days					
Sex	Olanzapine Dose (mg/kg/day)	RDC-0313 Dose (mg/kg/day)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>(0-24)</sub> (ng*hr/mL)
Day 1					
Male	5	0	102	4.80	966
	1.5	3	30.6	4.67	243
	5	10	102	5.60	1200
Female	5	0	169	2.80	1160
	1.5	3	35.7	4.67	284
	5	10	86.9	6.40	1060
Day 91					
Male	5	0	237	4.40	1910
	1.5	3	32.4	6.00	362
	5	10	211	6.40	2250
Female	5	0	222	5.20	2030
	1.5	3	39.0	6.00	373
	5	10	192	6.00	2140

<sup>a</sup> Administered as the malic acid salt (RDC-0313-02) of the active moiety.  
AUC<sub>(0-24)</sub> = Area under the plasma concentration-time curve from time zero to 24 hours postdose.

## Dosing Solution Analysis

The concentrations of RDC-0313 in the dosing formulations were within 7% of the nominal concentration throughout the study (tested at weeks 1, 2, 3, 4, 8, and 12), with the exception of week 3 for the 0.60 mg/ml formulation (dose level 3 mg/kg/day) which was +11.3% (just slightly outside the acceptance range of ±10%).

## 7 Genetic Toxicology

### 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

**Study title:** Bacterial Reverse Mutation Assay

Study no.: AT-0313-04

Study report location: SDN 1

Conducting laboratory and location:

(b) (4)

Date of study initiation: March 28, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RDC-0313-02 (malic acid salt), lot no. 8BK0032F, 96.2%

**Key Study Findings:** RDC-0313-02 was negative in the Ames assay. Considered non-mutagenic under the condition of the assay.

### **Study Validity**

The assay was valid. Appropriate tester strains and positive controls were used, the positive controls produced reliable positive results and were within the historical control ranges for the laboratory, and an appropriate maximum concentration (5000 µg/plate) was used.

### **Results**

There were no statistically significant, or dose-related, increases in the number of revertant colonies compared to the negative control in any tester strain at any dose level. RDC-0313-02 is considered non-mutagenic under the conditions of this assay.

## Methods

Strains: *S. typhimurium* TA1535, 1537, TA98, and TA100, and *E. coli* WP2 *uvrA*

Concentrations in definitive study: 50, 150, 500, 1500, and 5000 µg/plate

Basis of concentration selection: An initial assay was conducted using a larger range of doses: 1.5, 5, 15, 50, 150, 500, 1500, and 5000 µg/plate. No precipitation was observed.

Negative control: DMSO

Positive control: -S9: TA98: 1.0 µg/plate 2-nitrofluorene; TA100, TA1535: 1.0 µg/plate sodium azide; TA1537: 75 µg/plate 9-aminoacridine; WP2 *uvrA*: 1,000 µg/plate methyl methanesulfonate  
+S9: All *Salmonella* Strains: 1.0 µg/plate 2-aminoanthracene; WP2 *uvrA*: 10 µg/plate 2-aminoanthracene

Formulation/Vehicle: DMSO

Incubation & sampling time: Plates were incubated for 48 to 72 hours at 37±2°C. Plates were run in duplicate with and without metabolic activation (rat liver S9). Plate incorporation method.

## 7.2 *In Vitro* Assays in Mammalian Cells

**Study title:** In Vitro Mammalian Chromosome Aberration Test

Study no.: AT-0313-05

Study report location: SDN 1

Conducting laboratory and location: (b) (4)

Date of study initiation: March 27, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RDC-0313-02, Lot # 8BK0032F, 96.2%

**Key Study Findings:** RDC-0313-02 was negative for the induction of structural and numerical chromosomal aberrations.

## Methods

Cell line: Human peripheral blood lymphocytes obtained from a healthy non-smoking 27 year old female for the preliminary toxicity assay and from a healthy non-smoking 23 year old female for the definitive assay.

Concentrations in definitive study: -S9: 25, 50, 250, 500, and 650 µg/mL

Basis of concentration selection: +S9: 25, 50, 250, 500, and 750 µg/mL  
Reduction in the mitotic index relative to the solvent control. At least 50% reduction in mitotic index relative to the solvent control was observed at concentrations ≥ 500 µg/mL in both non-activated 4 and 20-hour exposure groups and at concentration levels ≥ 1500 µg/mL in the S9-activated 4-hour exposure group.

Negative control: DMSO

Positive control: Mitomycin C (0.3 or 0.6 µg/mL) and cyclophosphamide (20 µg/mL)

Formulation/Vehicle: DMSO

Incubation & sampling time: -S9: 4 or 20 hours, +S9: 4 hours

### Study Validity

The study was considered valid. Appropriate positive controls were used, the positive controls produced reliable positive responses, the concentrations of test article tested were appropriate as they produced at least a 50% decrease in mitotic index.

### Results

There were no statistically significant, or dose-related, increases in the number of structural or numerical chromosomal aberrations under any of the testing conditions. RDC-0313-02 is considered non-clastogenic under the conditions of this assay.

### 7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

**Study title:** Mouse Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of RDC-0313-02

Study no: AT-0313-06

Study report location: SDN 1

Conducting laboratory and location:  (b) (4)

Date of study initiation: June 30, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RDC-0313-02; lot # 4036-A-R0-01-68-01; 91.9%

### Key Study Findings

RDC-0313-02 was negative in the micronucleus test using male ICR mice.

**Methods**

Doses in definitive study: 0, 42, 120, and 420 mg/kg  
 Frequency of dosing: Single oral administration  
 Route of administration: Oral gavage  
     Dose volume: 10 ml/kg  
 Formulation/Vehicle: Sterile water  
     Species/Strain: Mice/ICR/Males only for definitive assay  
     Number/Sex/Group: 5/group  
     Satellite groups: NA  
 Basis of dose selection: A range-finding study was conducted in male and female ICR mice (3/sex/group) using single oral doses of 35, 110, 350, 650, 875, or 1100 mg/kg. Mortality was observed at 650 mg/kg and 1100 mg/kg. Clinical signs of ataxia and tremors were observed at doses  $\geq 650$  mg/kg and 1100 mg/kg, respectively. Transient hypothermia was observed at 350 mg/kg, and a more pronounced ( $\geq 3^{\circ}\text{C}$ ) decrease in body temperature was observed for 5 hours or longer at 650, 875 and 1100 mg/kg. Toxicity was similar in males and females; therefore, only males were used in definitive study.  
     Negative control: Sterile water  
     Positive control: Cyclophosphamide 50 mg/kg

**Study Validity**

The study was considered valid because appropriate doses were used in the definitive assay, the number and species of animal was acceptable, the positive control elicited an appropriate positive response, the negative and positive control results were within the range of the historical control data for the laboratory.

**Results**

There was no statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCEs) per 10,000 PCEs in the drug-treated groups compared to the negative control. RDC-0313 is considered negative for the induction of micronuclei in vivo in male mice treated with a single oral dose of RDC-0313 up to 420 mg/kg.

**7.4 Other genotoxicity studies**

An Ames assay was conducted with potential impurity, (b) (4) because it was identified as equivocal in the Derek Nexus in silico prediction for mutagenicity.

Study Title/number: (b) (4) Bacterial Reverse Mutation Assay/ AT (b) (4) -01  
GLP and QA

Conducting Laboratory: [REDACTED] (b) (4)

Test article, lot no., potency: [REDACTED] (b) (4) Lot No.: ALN00140-006, 99.17%

Negative vehicle control: DMSO

Dose levels of test article in definitive assay: 100, 333, 1000, 3333 and 5000 µg/plate

Tester strains: *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 uvrA

The assay was adequately conducted. No precipitation or toxicity was observed in any tester strain at any concentration of the test article. [REDACTED] (b) (4) did not increase the number of revertant colonies compared to the negative vehicle control either in the presence or absence of metabolic activation (rat liver S9). Impurity [REDACTED] (b) (4) was negative in the Ames assay and is considered non-mutagenic under the conditions of this assay.

## 8 Carcinogenicity

Final carcinogenicity study reports for SAM were reviewed by ECAC under NDA [REDACTED] (b) (4)

[REDACTED] (b) (4) The ECAC meeting minutes are included in the appendix of this review (section 12).

All table and figures excerpted from Applicant's study report unless stated otherwise.

### 8.1 Two-year rat carcinogenicity study

#### Study title: 2-year oral (gavage) carcinogenicity study of RDC-0313 in Sprague-Dawley rats

Study no.:	AT-0313-26
Study report location:	SDN 1
Conducting laboratory and location:	[REDACTED] (b) (4)
Date of study initiation:	June 7, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RDC-0313-02 lots 1425-83-1 (96.4%), CMLW-391/10-AS7 (99.9%), CMLW-631/10-AS8 (99.1%), L1145L030 (99.7%)
CAC concurrence:	Yes: The study protocol was reviewed [REDACTED] (b) (4) and the meeting minutes were faxed September 4, 2018.

### Key Study Findings

- SAM (RDC-0313) was not carcinogenic in male rats by oral gavage up to the highest doses tested of 75 mg/kg/day and in females up to 60 mg/kg/day.
- Statistically significant decrease in survival rate for high dose females compared to controls.
- Significant decrease in body weight for males at all dose levels, correlated with a decrease in food consumption.
- Increased dose response trend for B-Fibroadenoma in the mammary gland for females.
- Safety margins at 75 mg/kg/day for males and 60 mg/kg/day for females are approximately 32 and 237 times, respectively compared to exposure at the MRHD of 10 mg SAM based on AUC at steady state.
- Sex differences in PK parameters for parent and metabolite (RDC-9986) ( $V_d$  and clearance higher in males than females) resulting in differences in exposure levels (higher exposure in females than males when adjusted for dose).

### **Adequacy of Carcinogenicity Study**

The carcinogenicity study was adequately conducted according to the protocol and protocol amendments. No deviations impacted study integrity.

### **Appropriateness of Test Models**

The species and strain used in the study (Sprague Dawley rat) is appropriate for long-term study and there is significant historical control data.

### **Evaluation of Tumor Findings**

A separate statistical review was conducted by Dr. Hepei Chen from the Division of Biometrics, her conclusion agreed with that of the Applicant that there was no statistically significant increase in tumors in the drug-treated groups compared to controls. The statistical review can be found in DARRTs under NDA (b) (4)

## Methods

Doses:	Males: 0, 20, 35, 75 mg/kg/day Females: 0, 15, 30, 60 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	5 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water
Basis of dose selection:	13-week and interim analysis of a 26-week repeat-dose toxicity studies.
Species/Strain:	Rats/Sprague-Dawley Crl:CD (SD) from (b) (4)
Number/Sex/Group:	70/sex/vehicle and high dose groups 1 and 4 60/sex/low and mid dose groups 2 and 3
Age:	At dosing initiation: 10 weeks old
Animal housing:	Individually housed
Paradigm for dietary restriction:	No, food and water <i>ad libitum</i>
Dual control employed:	No
Interim sacrifice:	Early termination due to mortality. See mortality section below for details.
Satellite groups:	Toxicokinetics: 9/sex/drug-treated groups, 3/sex/control groups
Deviation from study protocol:	Several protocol deviations were listed in detail. None of the deviations had major impact on the integrity of the study.

## Observations and Results

### Mortality

All female groups were terminated on day 664 and all male groups were terminated on days 666 and 667. This was based on advice from FDA/CDER.

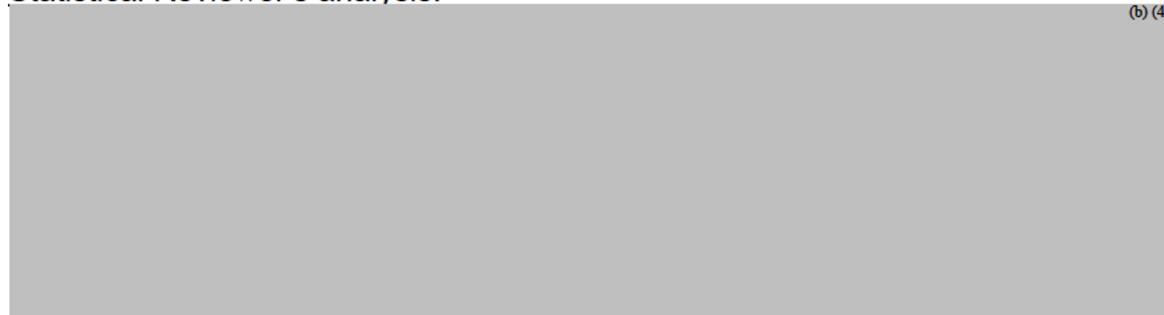
*“On April 13, 2012, the Applicant received agreement from FDA/CDER to immediately terminate all female dose groups based on current female survival values (Control — 14/70 (20%), Low Dose 8/60 (13%), Mid Dose — 17/60(28%), High Dose 6/70 (9%)). On this date, the Applicant also received FDA/CDER advice to terminate all male dose groups once male control rat survival reached 20 animals.”*

There were more early deaths for females compared to males, with most of the deaths due to moribund sacrifices (as compared to trauma or being found dead).

According to the Applicant, there was a statistically significant decrease in mean percent survival for high dose females compared to control females (7% and 19%, respectively). Conversely, there was a statistically significant increase in mean survival percent for low dose males (20 mg/kg/day) compared to control males (55% and 29%, respectively). The Applicant did not consider the effects on survival in high dose females and low dose males to be drug-related due to a lack of a dose-response in both

sexes, but rather due to biological variation. However, I do not agree because males and females had opposing effects on body weight and food consumption and most importantly vastly different exposure levels to both parent and metabolite. Since the toxicity and toxicokinetic profiles are different between males and females, it is possible that effects on survival rates would also be different. No drug-related cause of early deaths was identified for males or females.

Statistical Reviewer's analysis:



[Source: Dr. Hepei Chen's Statistical review under NDA (b) (4)]

Rats were 10 weeks old at the initiation of dosing, which is 2 to 4 weeks older than the suggested initial age of rats (6 to 8 weeks old) for a 2-year bioassay according to FDA Redbook 2006 and OECD guideline 2009. Although the Applicant does not believe that the initial age of the rats impacted the study results or interpretation of data, it is possible that the older initial age of the rats may have contributed to the increase in early deaths seen in this study across all groups, including controls, especially for females.

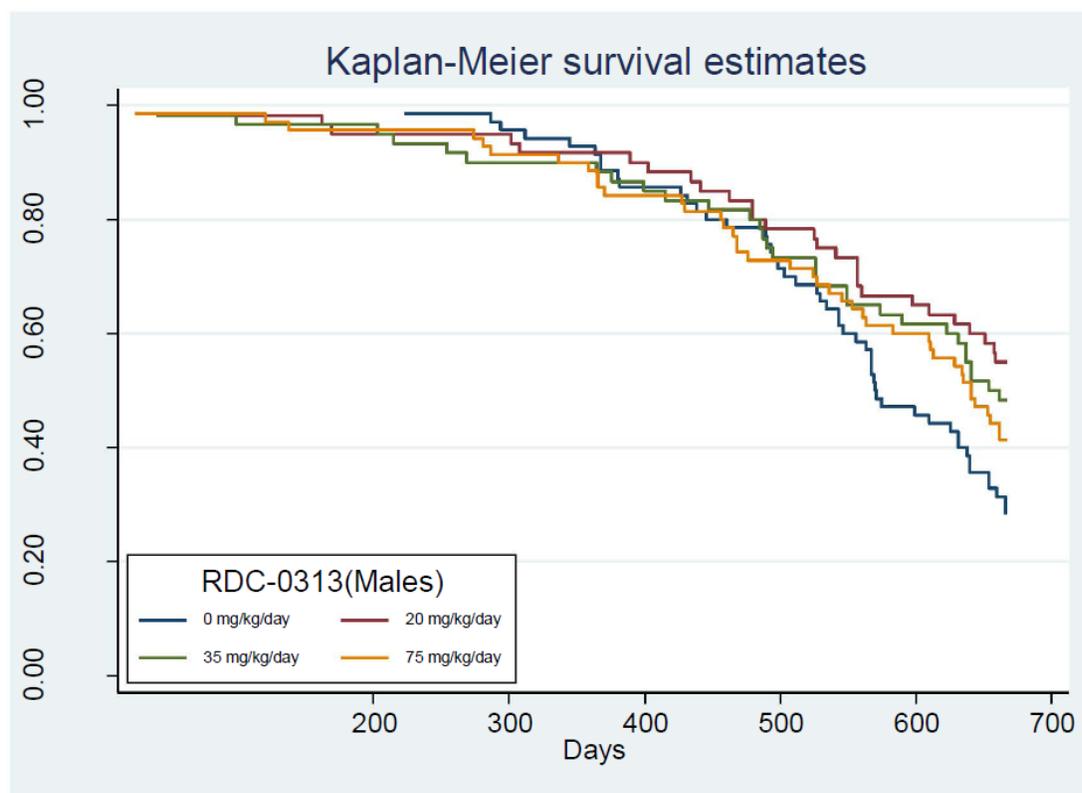
**Table 2. Summary of Early Deaths and Survival**

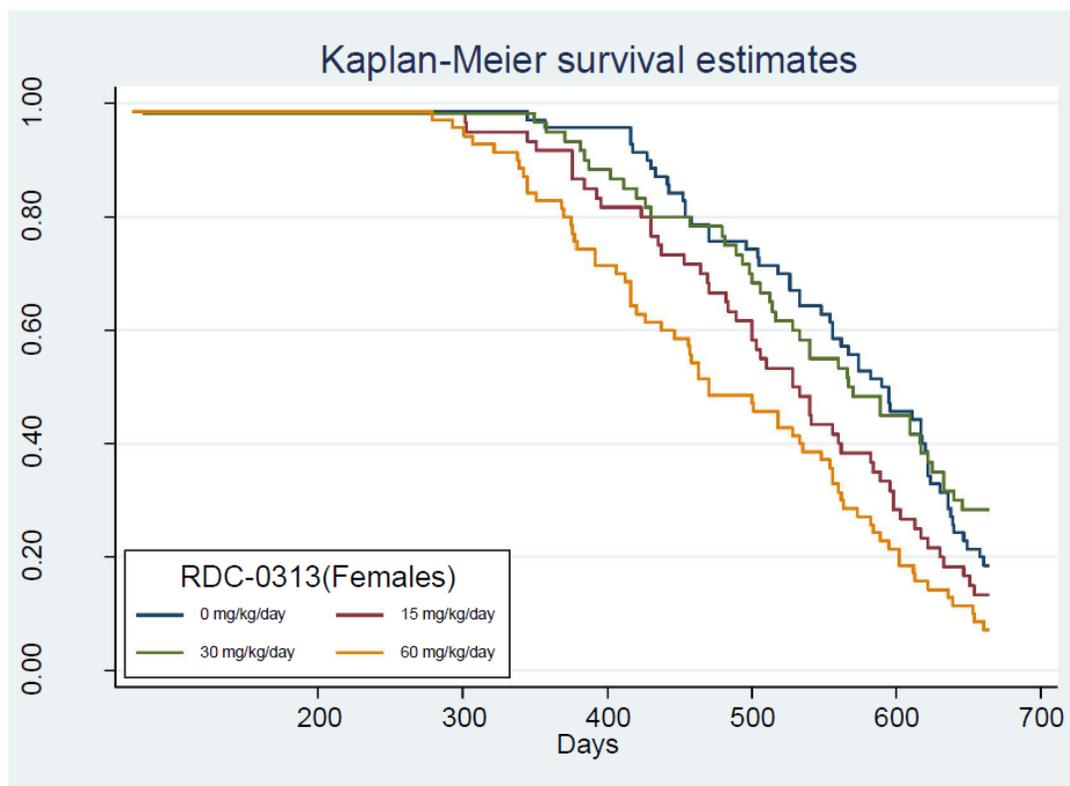
	Vehicle	Low	Mid	High
<b>Male</b>				
<b>No. Group</b>	<b>70</b>	<b>60</b>	<b>60</b>	<b>70</b>
<b>Unscheduled Deaths</b>	<b>50</b>	<b>27</b>	<b>31</b>	<b>41</b>
<b>Terminal Sacrifices (%)</b>	<b>20 (29%)</b>	<b>33 (55%)</b>	<b>29 (48%)</b>	<b>29 (41%)</b>
<b>Female</b>				
<b>No. Group</b>	<b>70</b>	<b>60</b>	<b>60</b>	<b>70</b>
<b>Unscheduled Deaths</b>	<b>57</b>	<b>52</b>	<b>43</b>	<b>65</b>
<b>Terminal Sacrifices (%)</b>	<b>13 (19%)</b>	<b>8 (13%)</b>	<b>17 (28%)</b>	<b>5 (7%)</b>

**Table 4. Summary of Selected Causes of Unscheduled Deaths in Male and Female Rats Following Oral Administration of RDC-0313<sup>a</sup>**

Dose Group mg/kg/day	Pituitary Neoplasms (% of Early Deaths)		Mammary Neoplasms (% of Early Deaths)		Cardiomyopathy <sup>a</sup> (% of Early Deaths)		Other Neoplasms <sup>b</sup> (% of Early Deaths)		Other COD <sup>c</sup> (% of Early Deaths)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0/0	24 (48)	48 (84)	2 (4)	3 (5)	6 (12)	0 (0)	12 (24)	3 (5)	6 (12)	3 (5)
20/15	18 (67)	43 (83)	0 (0)	6 (12)	2 (7)	0 (0)	5 (19)	2 (4)	2 (7)	1 (2)
35/30	16 (52)	38 (88)	2 (6)	2 (5)	0 (0)	0 (0)	8 (26)	1 (2)	5 (16)	2 (5)
75/60	20 (49)	53 (82)	1 (2)	6 (9)	3 (7)	1 (2)	6 (15)	3 (5)	11 (27)	2 (3)

- a. Cardiomyopathy proposed as the cause of death (coded only as moderate or marked severity) in a rat lacking a neoplasm as a cause of death (COD) (i.e., no neoplasm present to account for a proximate cause of death).
- b. Other neoplasms (non-pituitary, non-mammary) in early death rats; deemed the COD.
- c. Other causes of death (COD) include accidental death/trauma, inflammation (various sites), nephropathy, hernia, undetermined, hemorrhage, and perforation.
- d. In the absence of a fatal neoplasm (noted as "definitely fatal" in the microscopic observation tables), the COD was a subjective determination by the study pathologist and not recorded in the raw data.





## Clinical Signs

There were no drug-related clinical signs in females; all observed clinical signs were also observed in vehicle control females at a similar frequency. Fewer clinical signs were observed in males as compared to females; none were considered drug related. Alopecia on the ventral part of the body was observed in males at the mid and high doses only and may be drug-related. Excessive salivation and swelling of the foot was observed in mid and low dose males, respectively, but since there was no dose-related effect the finding is most likely incidental and not drug-related. There was also no clear drug-related increase in palpable masses for males or females compared to controls. The onset and location of masses was not dose dependent and was not considered drug-related, as findings in drug-treated groups were similar to control groups. However, the onset of palpable masses occurred early during the study in female groups compared to male groups and females also had a higher frequency of palpable masses compared to males. The prevalent location of palpable masses for females from all groups, including controls, was the lateral part of the body. Possibly due to the location of the masses, as they increased in size, rats had impaired mobility and/or difficulty breathing which caused limited access to food and/or water and contributed to the animals' moribund condition and subsequent early termination. Females had a much higher frequency of early deaths due to moribund sacrifice as compared to males. Detailed clinical signs, including mass palpitations, were conducted once a week up until week 26, and then conducted monthly thereafter.

**Summary of Common Clinical Observations**

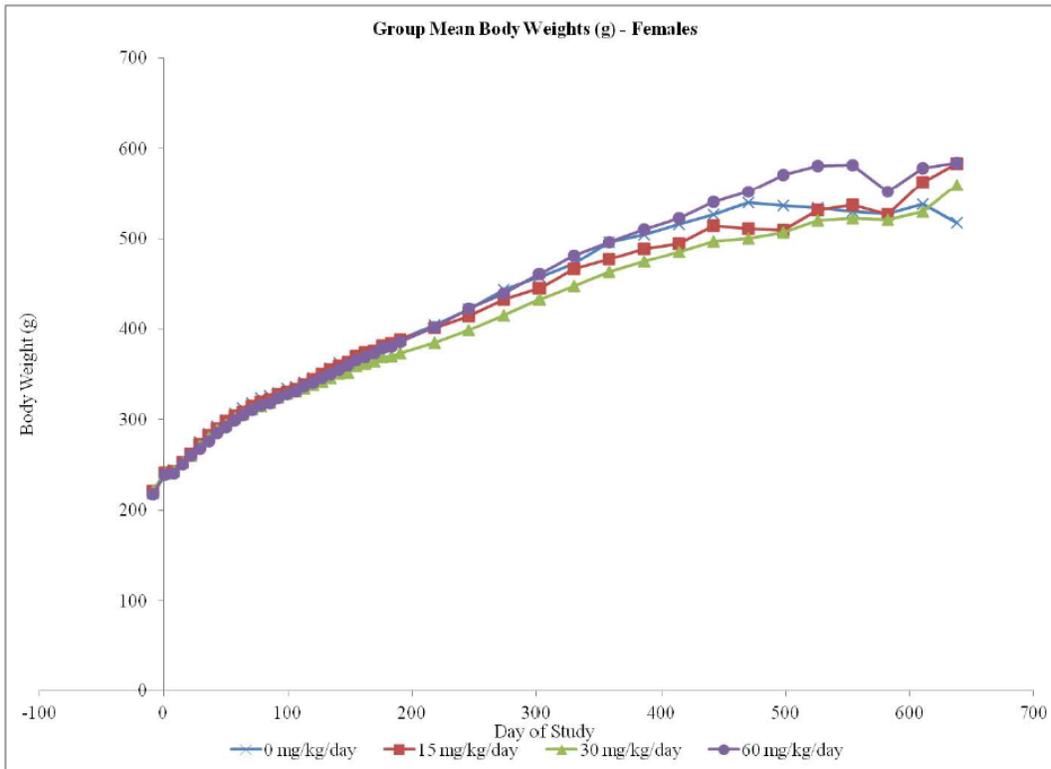
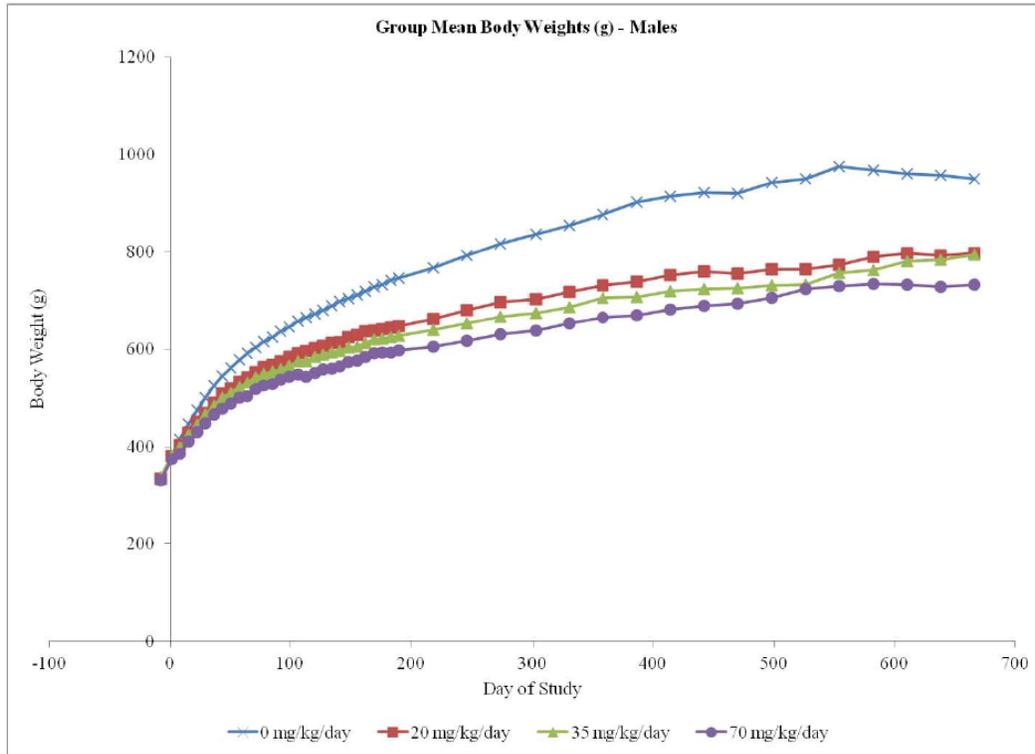
<b>Observation</b>	<b>Total Number of Males (mg/kg/day)</b>				<b>Total Number of Females (mg/kg/day)</b>			
	(0)	(20)	(35)	(75)	(0)	(15)	(30)	(60)
Abrasion hindlimb	11	11	11	--	10	9	--	0
Alopecia forelimb	13	13	11	11	14	14	12	7
Alopecia body ventral	--	--	6	4	--	--	--	--
Eye discharge red	--	--	--	--	31	--	--	--
Excessive salivation	0	--	11	--	0	0	0	--
Mass body lateral	--	--	--	--	29	22	30	24
Mass body ventral	--	--	--	--	18	13	--	19
Mass genitalia	0	0	0	0	13	--	--	--
Swelling foot	--	9	--	--	20	24	16	13

-- = Total number of observations  $\leq$  50.

0 = Observation not noted for this group.

**Body Weights**

There was a dose-dependent decrease in mean body weight for males throughout the entire study. At the end of the study on dosing day 666, there was a 16%, 16%, and 23% decrease in mean body weight compared to controls for surviving males at 20, 35, and 75 mg/kg/day, respectively. In contrast to males, there was no effect on body weight for females and mean weights were similar to, or slightly less than, controls during approximately the first 500 days of the study. Towards the end of the study, body weights for high dose females were increased compared to controls, but this effect was mainly attributed to a dramatic decrease in body weight in the control group. The effects on body weight correlated with effects on food consumption for males and females, most notably the sharp decrease in body weight for control females starting around day 500 correlated with a sharp decrease in food consumption during the same time period. Similarly, an increase in body weight occurred in high dose females starting after day 600 which also correlated with an increase in food consumption. Body weights were recorded prior to treatment, weekly through week 27, monthly starting in week 28, and the day prior to and the day of scheduled necropsy.



**Group Mean Body Weight Percent Difference from Vehicle Group - Males**

RDC-0313 Dose Group (mg/kg/day)	Day					
	1	29	92	183	358	666
	percent					
20	-0.31	-6.23	-9.67	-13.01	-16.64	-15.99
35	-0.03	-7.05	-12.10	-15.66	-19.51	-16.29
75	-1.62	-10.50	-15.50	-19.94	-24.05	-22.71

**Group Mean Body Weight Percent Difference from Vehicle Group - Females**

RDC-0313 Dose Group (mg/kg/day)	Day					
	1	29	92	183	358	638
	percent					
15	0.83	-0.80	-0.73	0.26	-3.85	12.80
30	0.58	-1.38	-1.58	-3.39	-6.71	8.14
60	-0.21	-2.47	-1.82	-0.63	-0.08	12.90

**Food Consumption**

There was a dose-related decrease in food consumption for males compared to controls which correlated directly with effects on body weight. There was no drug-related effect on food consumption for females, which also correlated with no drug-related effects on body weight. There was a decrease in food consumption for control females starting around study day 500, which directly correlated with a decrease in body weight for control females during that same time period.

Food consumption was recorded prior to dosing initiation, weekly until up week 27, and monthly thereafter.

**Ophthalmology**

There was no drug-related effect and the incidence rate of corneal crystals observed in males or females during study week 52 were not dose-related and and/or observed at a similar frequency in control animals. Ophthalmic exams were conducted once prior to dosing initiation on day -14 for males and -13 for females and then during week 52 on all surviving main study animals.

The presence of cataracts was also evaluated during scheduled and unscheduled necropsies as part of the histopathological exams. Cataracts were observed in one male at 20 mg/kg/day and in four males at 75 mg/kg/day from both the unscheduled and scheduled sacrifices (incidence rate of 4/70, 5.7%). The cataract incidence rate in this study was within the expected background range incidence for this rat strain (9.8% reported for Sprague-Dawley rats (Durand, G. 2001)). Therefore, cataract formation was not considered to be a drug-related finding.

**Clinical pathology**

There were no drug-related effects on any hematology, coagulation, or clinical chemistry parameters.

Blood samples for hematology, serum chemistry, and coagulation parameters assessments were collected from all surviving core subgroup rats on the days of scheduled necropsy prior to termination.

### Gross Pathology

Scheduled necropsy for female rats occurred on day 664. This was based on the number of live females [control = 14/70 (20%), low dose = 8/60 (13%), mid dose = 17/60 (28%), high dose = 6/70 (9%)] and FDA/CDER advice received on April 13, 2012. The Applicant terminated all male dose groups on days 666 and 667, because the survival of the control male group reached 20 rats on day 666. This was also based on FDA/CDER advice received on April 13, 2012.

There were statistically significant increases in organ-to-body weight ratios for brain, heart, kidney, liver, lung, and testes for males at all dose levels compared to controls. However, the effect was attributed to the lower group mean terminal body weights for males at all dose levels and not considered a direct drug effect.

### Histopathology

Peer Review: Yes. An internal peer review was performed.

#### Neoplastic

The Applicant concluded that there was an increasing dose response trend for B-Fibroadenoma in mammary gland in females, and a decreasing dose response trend for M-Carcinoma(tubular), in mammary gland. More rats in the treated groups died earlier and had mammary gland B-Fibroadenomas compared to controls. However, our statistician did not find such trend for these tumor types.

Tissue/ Diagnosis <sup>a</sup>	Tumor Type <sup>b</sup>	Number of Tumors Observed <sup>c</sup>				Significant Linear Trend <sup>d</sup>
		Vehicle	RDC-0313 (15 mg/kg/day)	RDC-0313 (30 mg/kg/day)	RDC-0313 (60 mg/kg/day)	
Mammary Gland B- Fibroadenoma	I	22	18	22	25	0.021618
	M	8	7	12	4	
Mammary Gland M-Carcinoma, tubular	I	4	3	2	1	0.016018
	M	2	2	0	0	
	F	1	0	0	0	

a. B = benign; M = Malignant.

b. M = mortality independent; I = incidental; F = fatal; "mortality independent" is treated as "incidental" in the tumor analysis.

c. For each tumor type in a tissue, only one tumor is counted if there are multiple tumors observed.

d. If the dose trends are significant at the 0.05 level, then the p-values were provided in this column.

#### Statistical Reviewer's Analysis:

[Source: Dr. Hepei Chen's Statistical review under NDA (b) (4)]

### Rare neoplasms:

Group: 1-Vehicle; 2-15 ♀/20 ♂ mg/kg/day; 3- 30 ♀/35 ♂ mg/kg/day; 4-60 ♀/75 ♂ mg/kg/day					
Observation/Tissue	Group:	Number Observed Per Group			
		1	2	3	4
<b>Males</b>					
Astrocytoma (brain)		2	0	2	1
Osteoma (bone)		0	0	1	0
Carcinoma (cecum)		1	0	0	0
Carcinoma (esophagus)		1	0	0	0
Schwannoma (heart)		0	0	1	0
Lipoma (kidney)		0	1	0	0
Leiomyoma (jejunum)		0	0	1	0
Carcinoma (jejunum)		0	0	0	1
Rhabdomyosarcoma (muscle)		1	0	0	0
<b>Females</b>					
Schwannoma (heart)		2	0	0	0
Leiomyoma (jejunum)		0	1	0	0
Lipoma (kidney)		2	1	1	0
Carcinoma (uterus)		0	0	1	0

### Non-Neoplastic

Drug- and dose-related hepatocellular cytoplasmic vacuolation was observed in males at 35 and 75 mg/kg/day. The vacuoles were described as being typical of a lipid: clear, round, variable in size (macro- and microvesicular), and sharply delineated. Similar vacuoles were also observed in low dose males, but at a similar incidence to control males. There was no drug-related increase in the incidence of hepatocellular cytoplasmic vacuolation in females. The severity level was similar across all dose groups for males and females. The increase in liver vacuoles only in drug-treated males and not females could be due to the difference in PK parameters of the drug and metabolite, including much higher exposure to metabolite RDC-9986 in males

compared to females. Hyperplasia of the pituitary gland, pars distalis, was observed at an increased incidence in high dose females compared to controls (11/65 compared to 6/57, respectively) and at an increased severity. Other incidental findings occurred in various dose groups and controls including increased lung alveolar macrophages, inflammation in various tissues, and acinar cell atrophy, but were considered incidental and not drug-related.

**Table 3. Summary of Selected Non-Neoplastic Graded Observations in the Liver – Males and Females (Core and Unscheduled)**

		Group: 1-Vehicle; 2-Low Dose; 3-Mid Dose; 4-High Dose			
Tissue/Observation	Group:	Number Observed Per Group			
		1	2	3	4
<b>Males</b>					
Liver					
Hepatocellular cytoplasmic vacuolization	Number Examined:	70	60	60	70
	Incidence	14	10	26	49
	Average Severity	(1.8) <sup>a</sup>	(1.8)	(1.8)	(1.9)
<b>Females</b>					
Liver					
Hepatocellular cytoplasmic vacuolization	Number Examined:	70	60	60	70
	Incidence	20	15	14	23
	Average Severity	(1.9)	(1.9)	(1.9)	(2.0)

a. Average severity equals sum of severity scores (core and unscheduled) divided by number of animals examined with this occurrence.

## Toxicokinetics

Whole blood samples were collected from toxicokinetic animals (3 rat/sex/group) on day 1 and 187 at 0.5, 1, 3, 8, and 24 hours after dosing.

The toxicokinetic profiles of parent (RDC-0313) and metabolite RDC-9986 were vastly different in males compared to females, which may contribute to differences observed in toxicities between the sexes (e.g., survival rates, effects on body weight and food consumption, and incidence of liver vacuoles). Exposure to RDC-0313 increased greater than dose proportional for males and females from the low to mid dose, and then roughly dose proportional from the mid to high dose. There was less than a 2-fold increase in exposure in males from day 1 to day 187, and a roughly 2-fold increase in exposure in females, indicating minimal drug accumulation for males and slight drug accumulation for females.

The main PK parameter that is different in males and females is volume of distribution, and consequently clearance rates. The volume of distribution for RDC-0313 is 4.5- to 10.1-fold and 6.7- to 22.5-fold greater in males compared to females on days 1 and 187, respectively. Clearance rates for RDC-0313 are similarly greater in males compared to females, 3.5- to 14.5-fold and 4.5- to 21.9-fold on days 1 and 187, respectively. Because of greater clearance rates of RDC-0313 in males, plasma exposure of RDC-0313 was markedly lower in males compared to females even at higher doses, e.g., day 187 AUC value of 11,800 ng.hr/ml in males at a dose of 75 mg/kg/day compared to 86,100 ng.hr/ml for females at a dose of 60 mg/kg/day.

The opposite sex effect on PK parameters was observed for the metabolite, RDC-9986. The volume of distribution and clearance were greater in females compared to males, 3- to 5-fold greater in females compared to males. As a result, plasma exposure of RDC-9986 was greater in males compared to females at higher doses.

### RDC-0313

**Table 2. TK Parameters for RDC-0313 on Day 1 Following Oral Administration of RDC-0313-02 to Rats<sup>a</sup>**

Gender	Target Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (ng/mL)/(mg/kg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*ng/mL)/(mg/kg)
Male	20	676	33.8	0.500	0.440	1.57	24,100	54,600	814	831	41.6
	35	2020	57.7	0.500	0.217	3.19	12,700	58,500	2750	2750	78.6
	75	3580	47.7	0.500	0.202	3.43	9740	48,300	7630	7700	103
Female	15	2350	157	0.500	0.483	1.44	2800	5790	5260	5370	358
	30	4470	149	0.500	0.184	3.77	1970	10,700	15,100	15,300	510
	60	5790	96.5	1.00	0.196	3.54	1660	8460	35,900	36,200	603

b. TK parameters were reported to three significant figures.

**Table 5. TK Parameters for RDC-0313 on Day 187 Following Oral Administration of RDC-0313-02 to Rats<sup>a</sup>**

Gender	Target Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (ng/mL)/(mg/kg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*ng/mL)/(mg/kg)
Male	20	440	22.0	0.500	0.218	3.18	15,200	69,900	1100	1310	65.5
	35	1010	28.9	3.00	0.206	3.36	6650	32,200	5230	5260	150
	75	2090	27.9	1.00	0.147	4.73	6180	42,200	11,800	12,100	161
Female	15	2730	182	1.00	0.285	2.43	1370	4790	11,000	11,000	733
	30	5700	190	0.500	0.284	2.44	882	3110	34,000	34,000	1130
	60	10,700	178	1.00	0.211	3.28	694	3280	86,100	86,500	1440

a. TK parameters were reported to three significant figures.

### RDC-9986 (Metabolite)

**Table 3. TK Parameters for RDC-9986 on Day 1 Following Oral Administration of RDC-0313-02 to Rats<sup>a</sup>**

Gender	Target Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (ng/mL)/(mg/kg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*ng/mL)/(mg/kg)
Male	20	1760	88.0	1.00	0.148	4.67	2410	16,200	8130	8300	415
	35	3070	87.7	0.500	0.159	4.35	2240	14,100	15,300	15,600	446
	75	4170	55.6	0.500	0.122	5.70	1790	14,700	39,900	41,900	559
Female	15	495	33.0	0.500	0.234	2.96	9090	38,900	1650	1650	110
	30	544	18.1	0.500	0.146	4.76	8330	57,200	3500	3600	120
	60	705	11.8	0.500	0.120	5.79	9840	82,200	5780	6090	102

a. TK parameters were reported to three significant figures.

**Table 7. TK Parameters for RDC-9986 on Day 187 Following Oral Administration of RDC-0313-02 to Rats<sup>a</sup>**

Gender	Target Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (ng/mL)/(mg/kg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Rate Constant (1/hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*ng/mL)/(mg/kg)
Male	20	963	48.2	0.500	0.152	4.57	2320	15,300	8440	8630	432
	35	1660	47.4	3.00	0.107	6.45	1940	18,100	16,600	18,000	514
	75	2940	39.2	1.00	0.0705	9.83	1720	24,400	35,400	43,600	581
Female	15	581	38.7	0.500	0.232	2.99	5340	23,000	2800	2810	187
	30	658	21.9	0.500	0.220	3.15	5900	26,800	5060	5080	169
	60	986	16.4	0.500	0.134	5.18	6010	44,900	9650	9980	166

a. TK parameters were reported to three significant figures.

Metabolite RDC-1066 was not measured in the carcinogenicity study, because it was determined to be a major human metabolite after completion of the carcinogenicity study. Exposure data for metabolite RDC-1066 was generated from a PK bridging study in rats (study AT-0313-41) and then exposure values at the doses used in the rat carcinogenicity study were estimated. A comparison of drug and metabolite exposures in rats to exposures in humans at the maximum recommended human dose (MRHD) of 10 mg SAM in the OLZ/SAM combination drug product are found in table 10 in section 11 of this review. Exposure of both metabolites are greater in male and female rats at the highest dose tested in the carcinogenicity study than in humans at 10 mg SAM.

### Dosing Solution Analysis

Concentrations of RDC-0313 in the dosing formulations analyzed ranged from 92.2 to 108.4% of the target concentration. No test article was detected in any vehicle control samples.

## 8.2 6-month transgenic mouse carcinogenicity study

### Study title: RDC-0313-02: 26-week repeated-dose oral carcinogenicity study in Tg.rasH2 mice

Study no.:	AT-0313-37
Study report location:	SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 28, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RDC-0313-02 (samidorphan L-malate), lot no. E528FP-13-001MS, 100%
CAC concurrence:	Yes, study protocol meeting minutes faxed January 30, 2014, under IND (b) (4). Final study report meeting minutes faxed September 4, 2018 under NDA (b) (4)

### Key Study Findings

- Not carcinogenic up to 500 mg/kg/day in male and female Tg.rasH2 mice
- Statistically significant increase in mortality for low and mid dose males, and high dose females compared to respective controls

### Adequacy of Carcinogenicity Study

Adequate. There was a statistically significant increase in the incidence of lung and spleen tumors in the positive control group, 1000 mg/kg/day urethane, demonstrating a response in the test system.

### Appropriateness of Test Models

The Tg.rasH2 mouse model is an acceptable model to use in short-term carcinogenicity assays as an alternative to the traditional two-year mouse carcinogenicity (ICH S1B).

### Evaluation of Tumor Findings

A separate statistical review was conducted by Dr. Hepei Chen from the Division of Biometrics, her conclusion agrees with that of the Applicant that there was no statistically significant increase in tumors in the drug-treated groups compared to controls. The statistical review can be found in DARRTs under NDA (b) (4)

## Methods

Doses:	0, 125, 250, 500 mg/kg/day
Frequency of dosing:	Once daily for up to 26 weeks
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water for injection
Basis of dose selection:	Dose selection was based on CNS clinical signs (i.e. ataxia and tremors) and/or morbidity observed in two 4-week wild type mouse studies.
Species/Strain:	Mouse/Tg.rasH2 mice (CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras)) from Taconic Farms Inc., Germantown, NY
Number/Sex/Group:	25/sex/group
Age:	At dosing initiation: 7 week old
Animal housing:	Individually housed
Paradigm for dietary restriction:	NA
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	Toxicokinetics: Non-transgenic wild-type littermates (CByB6F1 mice) 38/sex/groups 2-4, 8/sex/vehicle control group Positive control group 1000 mg/kg urethane in 0.9% saline; 10/sex, received 3 intraperitoneal injections on days 1, 3, and 5.
Deviation from study protocol:	None that affected study integrity.

## Observations and Results

### Mortality

There were non-dose dependent drug-related early deaths in males at all dose levels, 9/25, 9/25, and 2/25 at 125, 250, and 500 mg/kg/day, respectively reaching statistical significance in low and mid dose groups, compared to only one early death in the control group. The deaths began as early as day 16 after initiation of dosing. In contrast, statistically significant drug-related deaths in females occurred only in high dose (9/25) compared to only one death in the control group, and occurred later in the study, day 89. Similar to main study male animals, there was a large number of early deaths in the low dose and mid dose male toxicokinetic cohorts; 10/20 and 5/20, respectively compared to none in the control and high dose TK male groups. There were no unscheduled deaths in any of the female toxicokinetic groups. All early deaths were drug-related and not associated with dosing errors. The Applicant also initiated an investigation into other factors that might have contributed to the early mortality (e.g., formulations, animal room conditions) and concluded there were no abnormal room conditions and all formulations were accurately prepared. Since mortality was also observed in animals from the toxicokinetic cohorts, which consisted of wild-type littermates, the early deaths were not due to a finding unique to the transgenic animals.

The cause of death was undetermined for most of the males and for all females. However, it is likely that the cause of death is different for males and females due to different dose-response and temporal relationships.

**Text Table 1A: Main Cohort Mortality and Cause of Death**

Sex	Group (RDC-0313 Dose)	Animal No.	Mode of Death	Day of Death	Cause of Death
M	1 (0 mg/kg/day)	3925	Moribund Sacrifice	164	Lung, carcinoma
		3929	Natural Death	116	Undetermined
	3933	Natural Death	129	Undetermined	
	3935	Natural Death	133	Undetermined	
	3940	Moribund Sacrifice	29	Undetermined	
	3942	Natural Death	56	Undetermined	
	2 (125 mg/kg/day)	3947	Natural Death	16	Prostate gland inflammation, moderate and seminal vesicles, inflammation, marked
		3949	Moribund Sacrifice	121	Undetermined
		3950	Natural Death	48	Prostate gland and seminal vesicles; inflammation; marked
		4365	Natural Death	81	Undetermined
		3951	Natural Death	138	Undetermined
	3 (250 mg/kg/day)	3953	Moribund Sacrifice	26	Prostate gland; inflammation; moderate
		3954	Natural Death	58	Undetermined
		3958	Natural Death	32	Undetermined
		3961	Natural Death	49	Undetermined
		3962	Natural Death	163	Undetermined
		3970	Moribund Sacrifice	82	Undetermined
		3973	Natural Death	20	Undetermined
		3974	Natural Death	55	Undetermined
	4 (500 mg/kg/day)	3994	Moribund Sacrifice	57	Undetermined
		3999	Moribund Sacrifice	156	Prostate gland and seminal vesicles; inflammation; moderate

Natural Death = Found Dead

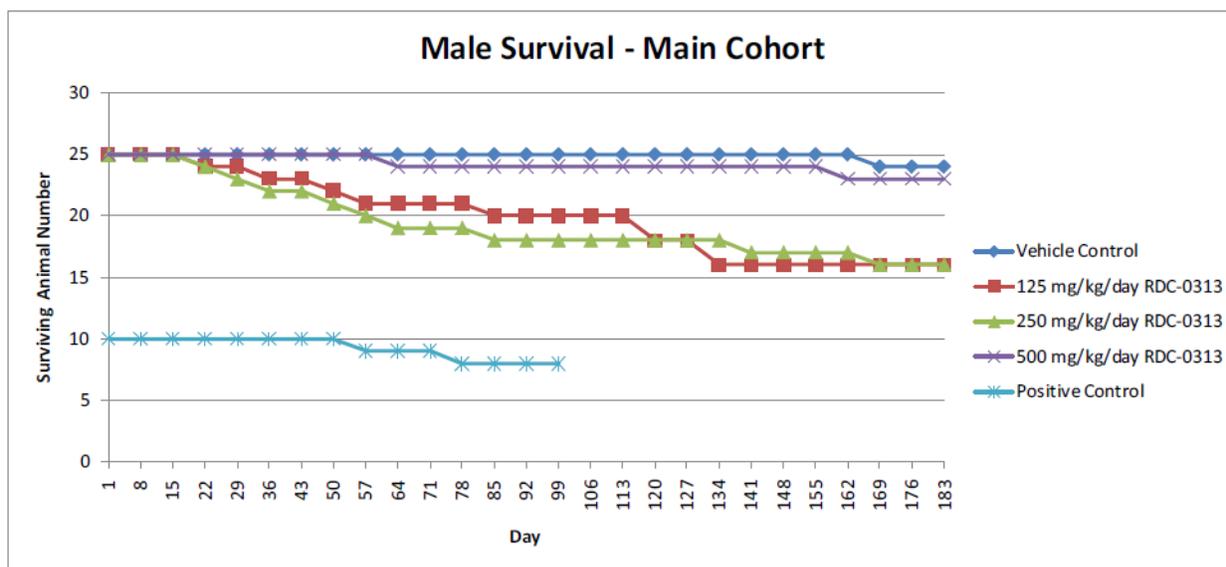
M = Male

**Text Table 1A: Main Cohort Mortality and Cause of Death (Continued)**

Sex	Group (RDC-0313 Dose)	Animal No.	Mode of Death	Day of Death	Cause of Death
F	1 (0 mg/kg/day)	4031	Moribund Sacrifice	156	Vagina, squamous cell carcinoma
		4090	Moribund Sacrifice	136	Undetermined
	4 (500 mg/kg/day)	4093	Natural Death	180	Undetermined
		4094	Moribund Sacrifice	111	Undetermined
		4097	Moribund Sacrifice	111	Undetermined
		4101	Natural Death	89	Undetermined
		4102	Moribund Sacrifice	142	Undetermined
		4107	Moribund Sacrifice	98	Undetermined
		4108	Natural Death	95	Undetermined
		4109	Natural Death	133	Undetermined

Natural Death = Found Dead

F = Female



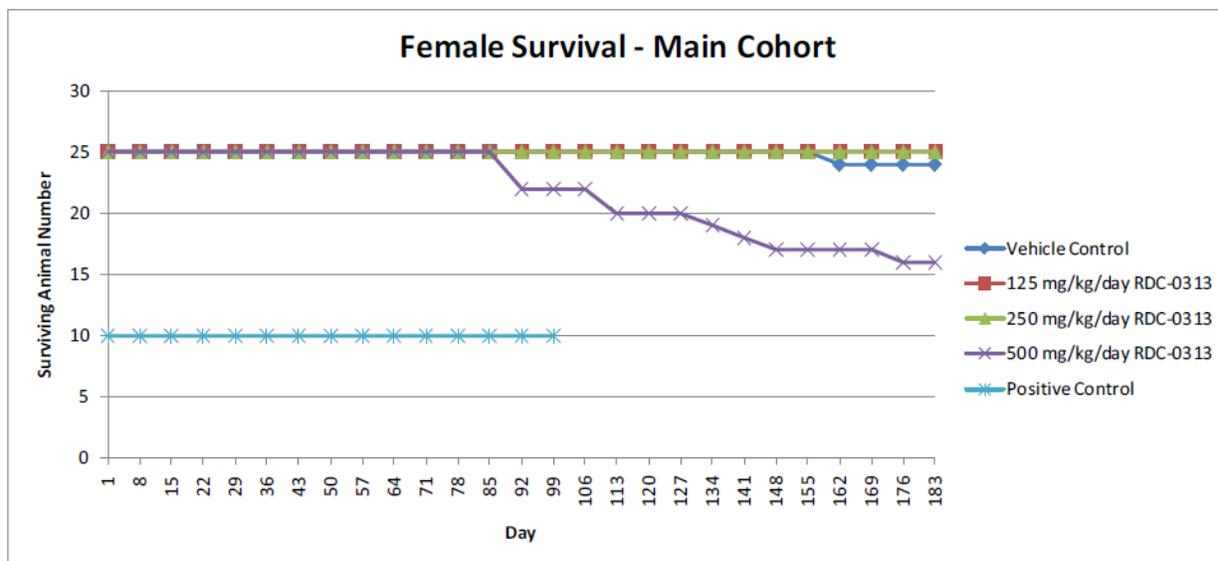
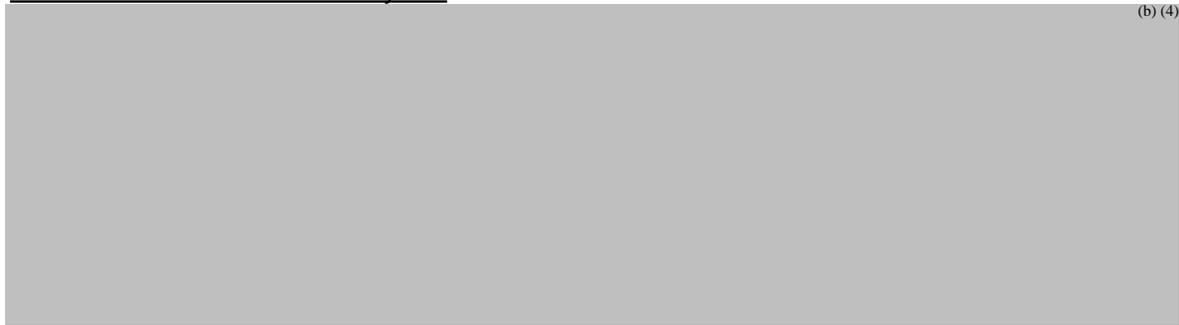


TABLE 1B - SUMMARY OF MORTALITY, TK COHORT

MALES

	Group:	Group 1 Vehicle Control 0 mg/kg/day	Group 2 125 mg/kg/day	Group 3 250 mg/kg/day	Group 4 500 mg/kg/day
Day 1 or Day 2	Scheduled Sacrifice	3	18	18	18
Day 21	Natural Death	-	-	1	-
Day 34	Moribund Sacrifice	-	1	-	-
Day 37	Natural Death	-	1	-	-
Day 39	Moribund Sacrifice	-	1	-	-
Day 44	Natural Death	-	1	-	-
Day 49	Natural Death	-	1	1	-
Day 50	Moribund Sacrifice	-	2	-	-
Day 56	Natural Death	-	-	1	-
Day 59	Natural Death	-	1	-	-
Day 60	Natural Death	-	1	-	-
Day 74	Natural Death	-	1	-	-
Day 79 or Day 80	Scheduled Sacrifice	-	10	-	-
Day 83	Moribund Sacrifice	-	-	1	-
Day 96	Moribund Sacrifice	-	-	1	-
Day 177 or Day 178	Scheduled Sacrifice	5	-	15	20
<b>Total Unscheduled Deaths</b>		<b>0/5</b>	<b>10/20</b>	<b>5/20</b>	<b>0/20</b>

Statistical Reviewer's Analysis:



(b) (4)

[Source: Dr. Hepei Chen's Statistical review under NDA (b) (4)]

The Applicant sent an email to Division on October 20, 2014, and subsequent submission to the IND, regarding premature deaths in the ongoing study.

*“Question for the Agency: Since deaths have occurred sporadically during the study as a contingency plan Alkermes is proposing to set the number of mice/sex/dose group at 15 to trigger the termination of that specific group.*

*Does the Agency agree with the proposal to terminate a Main Study dose group when the number of surviving animals is reduced to 15?”*

After internal discussion with members of the Executive Carcinogenicity Assessment Committee (Drs. Paul Brown and Abby Jacobs), the following comments for the Applicant were agreed upon and sent via email on October 23, 2014.

*“As we noted previously (e-mail on August 22, 2014), there is no defined minimum number of animals within a treatment for a 6-month transgenic mouse carcinogenicity study. Large numbers of premature deaths need an explanation, especially when not dose related. It is unclear at this time if the study will be adequate for assessment of carcinogenicity. The inverted dose response for mortality in males may make interpretation particularly challenging. Sacrifice of the low dose males when the group reaches 15 animals may be reasonable because the utility of this group would only be further limited with even lower numbers. However, the interpretability of the study will be determined once completed and submitted. In addition, a proposed mechanism for the inverted dose response for mortality and explanation of the cause of deaths should be included in the final study report.”*

**Applicant's proposed mechanism for inverted dose response for mortality in males.**

Although a cause of early deaths has not been explicitly determined in this study, mechanisms leading to death in male and female mice appear to be different for males and females based on different dose-response and temporal relationships of the mortality. Some mechanisms might be mouse specific and directly linked to differences in the formation of the metabolite RDC-9986 after treatment with RDC-0313. Specifically, at the lower doses (125 and 250 mg/kg/day), it is possible that the higher ratio of RDC-9986 to RDC-0313 coupled with high urinary excretion of the metabolite in male mice leads to a local imbalance within the genitourinary system favoring  $\mu$  opioid receptor agonist actions in the bladder of male mice; these latter changes presumably could lead to moribundity and ultimately death. At the higher dose (i.e., 500 mg/kg/day), there is enough systemic RDC-0313 available to effectively antagonize activity of the agonist activity of RDC-9986, but not completely at the lower doses. In contrast, females produce far less RDC-9986 at the lower dose and the systemic concentrations of RDC-0313 are sufficient to prevent local effects on the bladder. In females, it appears likely that differences in exposure relative to males (i.e., greater exposure to RDC-0313; lower exposure to RDC-9986) favor the antagonist activity of RDC-0313 (e.g., similar to the 500 mg/kg/day males). A reason for early deaths in the 500 mg/kg/day females is still unknown.

[Source: NDA 213378, study report AT-0313-37]

Supporting data for the Applicant's hypothesis includes TK data on the ratio of metabolite RDC-9986 to parent drug in males and females at each dose level. Also, data from in vitro receptor binding and functional assays revealed that the parent, RDC-0313, binds with high affinity to human  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors ( $K_i$  values of 0.052 nM, 0.23 nM, and 2.7 nM, respectively) and acts primarily as an antagonist at  $\mu$  receptors ( $IC_{50}$  value of 0.88 nM), and as a partial agonist/partial antagonist at  $\kappa$ - and  $\delta$ -receptors ( $EC_{50}$  values of 3.2 nM and 1.8 nM and  $IC_{50}$  values of 38 nM and 6.9 nM at  $\kappa$ - and  $\delta$ -receptors, respectively (study report no. 702-03231). In contrast, metabolite RDC-9986 binds to  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors with 10 to 100-fold lower affinity ( $K_i$  values of 0.26 nM, 23 nM, and 56 nM, respectively) but functionally acts as an agonist at all receptors ( $EC_{50}$  values of 17 nM, 53 nM, and 130 nM, respectively) (study report no. 702-03234-01). Additionally, in a hot-plate anti-nociceptive assay, metabolite RDC-9986 functioned as an agonist in mice but not in rats (study report nos. LSC14-233 and LSC12-066). Urinary excretion is the major elimination route of RDC-9986 in rats (study report no. 032317).

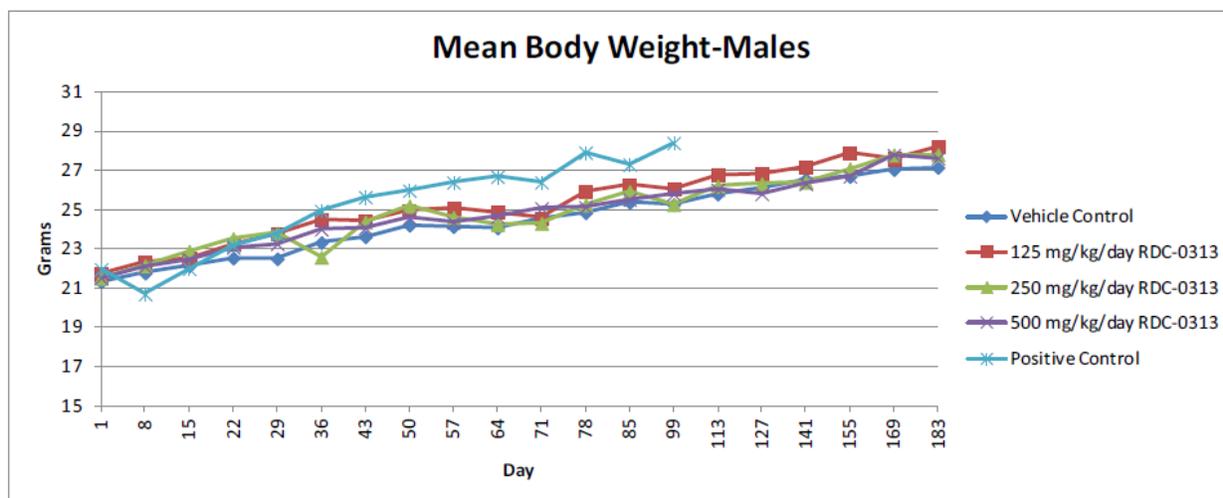
### Clinical Signs

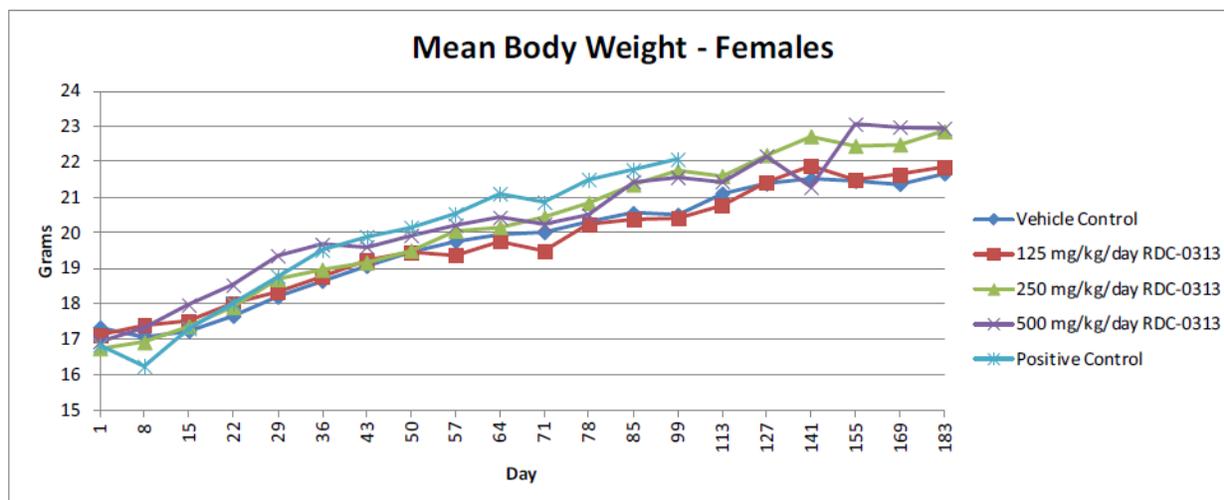
CNS-related clinical signs were observed in a dose-dependent manner in males and females and included hypersalivation (observed cageside) in 1/25, 12/25 and 19/25 males at 125, 250, and 500 mg/kg/day respectively, and in 4/25 and 13/25 females at 250 and 500 mg/kg/day. Hands-on observations of hypersalivation were observed in 2/25 and 5/25 males at 125 and 500 mg/kg/day, respectively, and 7/25, 4/25 and 10/25 females at 125, 250, and 500 mg/kg/day, respectively. Ocular discharge was also observed at 500 mg/kg/day in 8/25 and 5/25 males and females, respectively. Some clinical signs were observed predominantly in males. These included decreased motor

activity which was observed sporadically in 3/25 and 11/25 males at 250 and 500 mg/kg/day, respectively and tremors which were observed in 2/25 and 4/25 males at 125 and 500 mg/kg/day, respectively and in only 1 female at 500 mg/kg/day. Due to the sex difference in the toxicokinetic (TK) profile for both parent and metabolite (see TK section below), it is possible that the CNS signs which were observed at a higher incidence in males are due to increased plasma levels of metabolite RDC-9986. Cageside observations were performed on dosing days within 2 hours after the last animal in each group was doses. Detailed hands-on observations were conducted on day 1 and weekly thereafter in the main study groups.

### Body Weights

There was a statistically significant increase in absolute body weight at the end of the dosing period on study day 183 for females at 250 of 5% and a non-statistically significant increase of 6% compared to controls at 500 mg/kg/day. Overall body weight gain was also statistically significantly increased for females at 250 and 500 mg/kg/day, 41% and 38% compared to controls, respectively. The effect on body weight in females (but not in males), correlated with an increase in food consumption and was considered drug-related. There was no statistically significant, or dose-related, effect on body weight for males.





### Food Consumption

There was a statistically significant and dose-related increase in overall mean food consumption for males at all dose levels, 17% to 37% compared to controls. However, this increase did not correlate to increase in body weight gain. There was also a statistically significant increase in overall mean food consumption for females at 250 and 500 mg/kg/day of 19% and 32% compared to controls, respectively. The increase in food consumption for females correlated with an increase in body weight at 250 and 500 mg/kg/day.

### Ophthalmology

There were no drug-related ophthalmic lesions.

Eye exams were conducted by a veterinary ophthalmologist on main study animals twice pretreatment and on study days 171 and 169 for males and females, respectively.

### Organ / Tissue weights and Gross Pathology

Enlarged and dilated urinary bladders were observed in males from all dose groups, 10/25, 10/25, and 3/25 at 125, 250, and 500 mg/kg/day, respectively compared to none in the control group. This finding was considered drug-related and correlated with microscopic findings in the urinary bladders of males at all dose levels.

Absolute and relative adrenal gland weights were statistically significantly increased for males at 500 mg/kg/day, 25% compared to controls and correlated with adreno-cortical hypertrophy observed microscopically. Statistically significant increases in absolute and relative liver weights at 500 mg/kg/day for both males and females correlated with lipid infiltration observed microscopically. Absolute and relative ovary weights were statistically significantly decreased at all dose levels 25% to 40% compared to controls, and the effects correlated with microscopic findings of decreased corpora lutea at 500 mg/kg/day only. All other statistically significant changes in organ weights (heart, kidney, brain, spleen) did not correlate with any microscopic findings, therefore the toxicological relevance is not known.

TK animals were not necropsied.

Parameter	Sex	RDC-0313 Dose Level (mg/kg/day)	Significant Difference compared to Control (Group 1) ↑ or ↓	% Difference from Group 1
Absolute Adrenals	M	500	↑*	25.6%
Absolute Heart		125	↑**	11.5%
Absolute Liver		500	↑**	9.3%
Relative Adrenals		500	↑*	24.9%
Relative Kidney			↓**	7.7%
Relative Liver			↑**	7.6%
Terminal Body weights	F	250, 500	↑*	6.2%, 5.9%
Absolute Brain		500	↓**	6.5%
Absolute Liver		125	↓*	7.8%
Absolute Spleen		500	↑**	18.5%
Absolute Ovaries		125, 250, 500	↓*: 500 **: 125 and 250	32.1%, 36.2%, 25.2%
Relative Brain		250, 500	↓*: 250; **: 500	6.9%, 11.9%
Relative Heart		250	↓*	9.0%
Relative Kidney		500	↓*	7.3%
Relative Liver		125	↓**	8.9%
Relative Spleen		500	↑**	12.4%
Relative Ovary		500	↓**	37.7%
Relative Ovary		125, 250, 500	↓**	33.6%, 40.6%, 29.7%

↑ = Statistically significant increase (\*: p<0.05 ; \*\*: p<0.01) when compared to Group 1.

↓ = Statistically significant decrease (\*: p<0.05; \*\*: p<0.01) when compared to Group 1.

M = Male; F = Female.

## Histopathology

Tissues from all animals of groups 1-4, including early deaths, and the lungs and spleens from group 5 (positive control) were examined microscopically.

Peer Review: Yes. A signed peer review statement from the peer review pathologist ( (b) (4) DVM, DACVP, FIATP) was included in the study report.

## Neoplastic

According to the Applicant, there was no statistically significant increase in the incidence of lung tumors, splenic tumors, or other tumor types in males or females from any dose group compared to controls. The incidence of all observed tumors in the drug-treated groups was within the historical control range for the laboratory. As expected, there was a statistically significant increase in lung and splenic tumors in the positive control male and female groups compared to controls.

**Text Table 3: Incidence of Lung Tumors**

MALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR Incidence Range
Adenoma, single	2	2	2	1	0	0-6
Adenoma, multiple	0	0	0	0	10*	0-2
Carcinoma	1	0	0	0	2	0-2
Animals with tumors	3	2	2	1	10*	NA
FEMALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR Incidence Range
Adenoma, single	0	1	0	3	0	0-6
Adenoma, multiple	0	0	0	0	10*	0-1
Carcinoma	0	0	1	0	4	0-2
Animals with tumors	0	1	1	3	10*	NA

Group 1 - 0 mg/kg/day (Vehicle)

Group 2 - 125 mg/kg/day

Group 3 - 250 mg/kg/day

Group 4 - 500 mg/kg/day

Group 5 - 1000 mg/kg/day (positive control)

\* Statistically significant ( $p < 0.01$ ) when compared to vehicle control, 0 mg/kg/day (See [Appendix A](#)).HCR: BioReliance Historical Control Range (Incidence Range) for vehicle control mice (See [Appendix B](#)).

NA: Not applicable.

**Text Table 4: Incidence of Spleen Tumors**

MALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR Incidence Range
Hemangiosarcoma	1	0	1	1	8*	0-4
FEMALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR Incidence Range
Hemangiosarcoma	0	3	0	1	9*	0-4

Group 1 - 0 mg/kg/day (Vehicle)

Group 2 - 125 mg/kg/day

Group 3 - 250 mg/kg/day

Group 4 - 500 mg/kg/day

Group 5 - 1000 mg/kg/day (positive control)

\* Statistically significant ( $p < 0.01$ ) when compared to vehicle control, 0 mg/kg/day (See [Appendix A](#)).HCR: BioReliance Historical Control Range (Incidence Range) for vehicle control mice (See [Appendix B](#)).**Statistical Reviewer's Analysis:**

(b) (4)

[Source: Dr. Hepei Chen's Statistical review under NDA (b) (4)]

#### Non-Neoplastic

There were several drug-related non-neoplastic findings in both males and females. Most males from all dose groups (21 to 23 males/group) had adreno-cortical hypertrophy compared to none in control males, and the severity level increased with increasing dose. This finding correlated with increased adrenal gland weights in males at 500 mg/kg/day. There was also an increase in both incidence and severity of males with X-zone degeneration in the adrenal glands across all dose groups compared to controls. Urinary bladder dilation was observed in males from all drug-treated groups, but the incidence and severity were reverse dose-related, with the greatest incidence observed in low and mid dose groups and less in the high dose group. However, there were no pathological changes associated with it, for example, necrosis, degeneration and/or hyperplasia or neoplasia. Similarly, dilation of cortical tubules in the kidneys was observed in 8/25, 9/25, and 1/25 in the 125, 250, and 500 mg/kg/day males, respectively, which the Applicant suggested may be secondary to back flow of the urine. Urinary bladder dilation was not observed in any drug-treated females. Prostate gland inflammation was observed in 4 and 5 low and mid-dose respectively, compared to only 2 high dose males.

Several findings were observed in female reproductive organs at 250 and 500 mg/kg/day, including decreased corpora lutea, uterine and mammary gland atrophy, and mucification in the vagina. Males at 500 mg/kg/day and females at 250 and 500 mg/kg/day had infiltration of lipid in the liver which correlated with increased liver weights at 500 mg/kg/day in males and females.

## Toxicokinetics

Non-transgenic wild-type littermates (CByB6F1 mice) were used in the toxicokinetic cohort. Animals were bled on days 1, 79, and 177.

It should be noted that drug plasma exposure data from transgenic mouse carcinogenicity studies are not routinely used to calculate safety margins due to possible differences in metabolism with this strain of mice.

Day	RDC-0313 TK Parameter	RDC-0313 Dose, mg/kg/day					
		Male			Female		
		125	250	500	125	250	500
1	C <sub>max</sub> , ng/mL	4,650	8,400	19,800	10,700	16,500	53,600
	T <sub>max</sub> , h	1.00	1.00	1.00	1.00	1.00	2.00
	AUC <sub>(0-T)</sub> , ng·h/mL	6,940	20,600	81,600	36,500	70,500	213,000
	AUC <sub>(0-24)</sub> , ng·h/mL	7,000	20,600	81,600	36,500	70,500	213,000
	AUC <sub>(0-inf)</sub> , ng·h/mL	6,980	20,600	82,000	36,500	NC	225,000
	T <sub>1/2</sub> , h	1.21	2.30	3.21	2.37	NC	6.42
	C <sub>max</sub> Ratio (M/F)	0.435	0.509	0.369	-	-	-
AUC <sub>(0-24)</sub> Ratio (M/F)	0.192	0.292	0.383	-	-	-	
79*	C <sub>max</sub> , ng/mL	2,480	-	-	-	-	-
	T <sub>max</sub> , h	1.00	-	-	-	-	-
	AUC <sub>(0-T)</sub> , ng·h/mL	6,170	-	-	-	-	-
	AUC <sub>(0-24)</sub> , ng·h/mL	6,610	-	-	-	-	-
	T <sub>1/2</sub> , h	1.97	-	-	-	-	-
	C <sub>max</sub> Ratio (Day 79/Day 1)	0.533	-	-	-	-	-
AUC <sub>(0-24)</sub> Ratio (Day 79/Day 1)	0.944	-	-	-	-	-	
177	C <sub>max</sub> , ng/mL	-	7,410	18,200	12,700	17,600	26,100
	T <sub>max</sub> , h	-	1.00	1.00	1.00	2.00	2.00
	AUC <sub>(0-T)</sub> , ng·h/mL	-	23,600	74,100	61,300	121,000	163,000
	AUC <sub>(0-24)</sub> , ng·h/mL	-	23,600	74,100	61,300	121,000	163,000
	T <sub>1/2</sub> , h	-	2.58	2.48	3.70	2.66	2.40
	C <sub>max</sub> Ratio (M/F)	-	0.421	0.697	-	-	-
	AUC <sub>(0-24)</sub> Ratio (M/F)	-	0.195	0.455	-	-	-
	C <sub>max</sub> Ratio (Day 177/Day 1)	-	0.882	0.919	1.19	1.07	0.487
AUC <sub>(0-24)</sub> Ratio (Day 177/Day 1)	-	1.15	0.908	1.68	1.72	0.765	
*Due to high mortality in the males dosed with the 125 mg/kg/day, blood samples were collected on Day 79 compared with Day 177 for other groups. - = Not Applicable NC - Not Calculated							

Day	RDC-9986 TK Parameter	RDC-0313 Dose, mg/kg/day					
		Male			Female		
		125	250	500	125	250	500
1	C <sub>max</sub> , ng/mL	7,040	11,600	14,900	2,360	3,020	4,890
	T <sub>max</sub> , h	1.00	1.00	2.00	1.00	2.00	2.00
	AUC <sub>(0-T)</sub> , ng·h/mL	23,300	49,700	129,000	9,820	17,000	48,600
	AUC <sub>(0-24)</sub> , ng·h/mL	23,300	49,700	129,000	9,820	17,000	48,600
	AUC <sub>(0-inf)</sub> , ng·h/mL	23,300	49,800	134,000	9,850	NC	57,400
	T <sub>1/2</sub> , h	1.80	2.59	5.21	2.95	NC	8.90
	C <sub>max</sub> Ratio (M/F)	2.98	3.84	3.05	-	-	-
	AUC <sub>(0-24)</sub> Ratio (M/F)	2.37	2.92	2.65	-	-	-
79*	C <sub>max</sub> , ng/mL	5,660	-	-	-	-	-
	T <sub>max</sub> , h	1.00	-	-	-	-	-
	AUC <sub>(0-T)</sub> , ng·h/mL	27,800	-	-	-	-	-
	AUC <sub>(0-24)</sub> , ng·h/mL	27,800	-	-	-	-	-
	T <sub>1/2</sub> , h	2.55	-	-	-	-	-
	C <sub>max</sub> Ratio (Day 79/Day 1)	0.804	-	-	-	-	-
	AUC <sub>(0-24)</sub> Ratio (Day 79/Day 1)	1.19	-	-	-	-	-
177	C <sub>max</sub> , ng/mL	-	8,800	15,300	1,530	3,280	9,680
	T <sub>max</sub> , h	-	1.00	1.00	1.00	2.00	1.00
	AUC <sub>(0-T)</sub> , ng·h/mL	-	44,900	96,100	8,620	24,500	69,500
	AUC <sub>(0-24)</sub> , ng·h/mL	-	44,900	96,100	8,620	24,500	69,500
	T <sub>1/2</sub> , h	-	2.50	3.02	4.16	3.36	2.96
	C <sub>max</sub> Ratio (M/F)	-	2.68	1.58	-	-	-
	AUC <sub>(0-24)</sub> Ratio (M/F)	-	1.83	1.38	-	-	-
	C <sub>max</sub> Ratio (Day 177/Day 1)	-	0.759	1.03	0.648	1.09	1.98
AUC <sub>(0-24)</sub> Ratio (Day 177/Day 1)	-	0.903	0.745	0.878	1.44	1.43	
<p>*Due to high mortality in the males dosed with the 125 mg/kg/day, blood samples were collected on Day 79 compared with Day 177 for other groups.            - = Not Applicable            NC = Not Calculated</p>							

**Text Table 15: Ratio of RDC-9986 to RDC-0313 by Plasma AUC**

Sex	Day	RDC-0313 Dose (mg/kg/day)	RDC-9986/RDC-0313 (AUC <sub>0-24</sub> )
Male	1	125	3.33
		250	2.41
		500	1.58
Female	1	125	0.27
		250	0.24
		500	0.23
Male	79	125	4.21
	177	250	1.90
		500	1.30
Female	177	125	0.14
		250	0.20
		500	0.43

### Dosing Solution Analysis

All dosing formulations analyzed were within the acceptance criteria range of 90.0 to 110.0% of target concentration. No test article was detected in any of the vehicle control samples.

## 9 Reproductive and Developmental Toxicology

All table and figures excerpted from Applicant's study report unless stated otherwise.

### 9.1.1 Male Fertility and Early Embryonic Development

**Study title:** RDC-0313: An oral study of fertility and early embryonic development to implantation in **male** rats, including a toxicokinetic evaluation

Study no.: AT-0313-24 (825-030)  
 Study report location: SDN 1  
 Conducting laboratory and location: (b) (4)

Date of study initiation: April 20, 2010  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: RDC-0313-02 (malate salt form of RDC-0313; Lot 1425-83-1), 96.4%

### Key Study Findings

- Body weights were significantly and dose-dependently decreased compared to controls at all dose levels for males.
- There were no drug-related effects on any male fertility parameters and there were no drug-related effects on early embryonic development.

- NOAEL for male fertility is highest dose tested of 100 mg/kg/day, which is approximately 16 times the MRHD of 10 mg SAM based on AUC.

## Methods

Doses:	<b>0, 10, 30, 100 mg/kg/day</b>
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water for injection, USP
Species/Strain:	Rat/ CD[CrI:CD(SD)] from [REDACTED] (b) (4)
	~10 weeks old at dosing initiation
Number/Sex/Group:	25 males/group; 25 females/group were untreated
Satellite groups:	Toxicokinetics: 3 control males and 6 males/drug-treated groups. Dosed same as main study males and were bled on day 28.
Study design:	Dosing began 28 days prior to pairing males with untreated females and continued throughout the mating period and postmating period until the day of euthanasia (day 65-66 of treatment).
Deviation from study protocol:	None that affected study integrity.

## Dose selection:

Dose selection was based on the results of 2-week, 13-week, and 26-week repeat-dose toxicity studies with RDC-0313, administered as the malate salt, RDC-0313-02, to rats.

## Observations and Results

### Mortality

No drug-related deaths. One male at 30 mg/kg/day was found dead on day 63. A large bolus of food was found lodged in the animal's esophagus and therefore the death was not considered drug-related. One TK male at 100 mg/kg/day was euthanized on day 27 due to an accidental injury to the mouth and jaw.

### Clinical Signs

Dose-dependent salivation was observed in 8, 13, and 21 males at 10, 30, and 100 mg/kg/day compared to none in control males. Soft feces were also observed in 4-6 males at each dose level, compared to none in control males. Unkempt appearance was noted for 1 male each at 10 and 30 mg/kg/day and for 7 males at 100 mg/kg/day compared to none in control males.

### Body Weight

There was a dose-dependent and statistically significant decrease in mean body weight and weight gain in males throughout the entire dosing period. At the end of dosing on

day 64, mean body weights were statistically significantly decreased 8%, 11%, and 13% compared to controls at 10, 30, and 100 mg/kg/day, respectively and mean body weight gain also decreased during the pre-mating phase from days 1-29 of 21%, 35%, and 39% compared to controls at 10, 30, and 100 mg/kg/day, respectively. The changes in body weights correlated with decreases in food consumption. Body weights for males were recorded on the day of dosing initiation and then twice weekly during the treatment period until the day of scheduled euthanasia. Females were weighed the day of pairing and twice weekly during the gestation period.

### Food Consumption

Food consumption for all treatment groups was decreased compared to controls throughout the dosing period. The decreased was statistically significant for males at 100 mg/kg/day throughout the entire dosing period, and for males at 10 and 30 mg/kg/day mainly during the first 3 weeks of dosing. The decrease in food consumption correlated with decrease in body weights. Food consumption was recorded for males twice weekly prior to pairing for mating. Food consumption was not recorded during the mating period but resumed on day 16 and recorded twice weekly.

### Toxicokinetics

Exposure to RDC-0313 increased almost dose proportionally from 10 to 30 mg/kg/day and greater than dose proportional from 30 to 100 mg/kg/day. Elimination half-life values were similar across all dose groups. Exposure (AUC) to metabolite RDC-9986 also increased almost dose proportionally.  $T_{max}$  values for both parent and metabolite were short, 0.5 to 2 hrs. Exposure to metabolite were 13x (LD), 10x (MD), and 6x (HD), the exposure of the parent.

**Table 2. TK Parameters for RDC-0313 on Day 28 Following Repeat Oral Administration of RDC-0313 to Male Rats<sup>a,b</sup>**

Dose (mg/kg/day)	Observed $C_{max}$ (ng/mL)	Observed $C_{max}$ /Dose (kg*ng/mL/mg)	Observed $T_{max}$ (hr)	Terminal Elimination Half-Life (hr)	$AUC_{last}$ (hr*ng/mL)	$AUC_{last}$ /Dose (hr*kg*ng/mL/mg)	$AUC_{\infty}$ (hr*ng/mL)	$AUC_{\infty}$ /Dose (hr*kg*ng/mL/mg)
10	129	12.9	0.500	2.07	276	27.6	282	28.2
30	395	13.2	1.00	2.97	1000	33.3	1050	35.1
100	2220	22.2	1.00	3.09	5840	58.4	5860	58.6

a. TK parameters were reported to three significant figures.

b. Animal 4121 was excluded from TK analysis.

### Metabolite RDC-9986:

**Table 3. TK Parameters for RDC-9986 on Day 28 Following Repeat Oral Administration of RDC-0313 to Male Rats<sup>a,b</sup>**

Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /Dose (hr*kg*ng/mL/mg)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng/mL/mg)
10	906	90.6	1.00	3.54	3730	373	3760	376
30	1570	52.3	1.00	3.84	9910	330	10,000	335
100	3450	34.5	2.00	5.46	33,000	330	34,700	347

a. TK parameters were reported to three significant figures.

b. Animal 4121 was excluded from TK analysis.

### Dosing Solution Analysis

All dosing formulations were within 99.5% to 103% of target RDC-0313 concentrations and were homogeneous.

### Necropsy

There was a statistically significant decrease in epididymides and testes weights relative to body weights at all dose levels and an increase in relative seminal vesicle weights at 100 mg/kg/day. However, these differences were attributed to the significantly lower final body weights observed at all treatment levels and not a direct drug-related effect. The following organs were weighed: epididymides, testes, prostate, and seminal vesicles.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

There were no drug-related effects on any male reproductive or fertility indices (mating, fertility, and fecundity index). There was no effect on the number of females that became pregnant; 2, 1, 0, and 2 females were not pregnant at 0, 10, 30, and 100 mg/kg/day, respectively. There was no drug-related effect on the copulatory interval (3.1, 3.0, 3.2, and 3.2 days at 0, 10, 30, and 100 mg/kg/day, respectively.) There were no drug-related effects on any sperm analysis parameters (motility, concentration, and percent abnormal sperm).

### 9.1.2 Female Fertility and Early Embryonic Development

**Study title:** RDC-0313: An oral study of fertility and early embryonic development to implantation in **female** rats, including a toxicokinetic evaluation

Study no.: AT-0313-25 (825-031)

Study report location: SDN 1

Conducting laboratory and location:

(b) (4)

Date of study initiation: May 21, 2010

GLP compliance: Yes

QA statement: Yes  
 Drug, lot #, and % purity: RDC-0313-02 (malate salt form of RDC-0313; Lot 1425-83-1), 96.4%

### Key Study Findings

- Maternal toxicity at 150 and 450 mg/kg/day included clinical signs of salivation, partial or completely closed eyelids, and stereotypic behaviors. Body weight gain was decreased at 30 and 150 mg/kg/day but increased at 450 mg/kg/day; changes correlated with changes in food consumption.
- At 450 mg/kg/day, estrous cycle lengths were increased, and the total number of estrous cycles were decreased.
- There were no effects on reproductive or fertility parameters, including mating and pregnancy outcome.
- NOAEL for general toxicity is 30 mg/kg/day, NOAEL for effects on fertility and reproductive parameters is 450 mg/kg/day, which is approximately 681 times the MRHD of 10 mg SAM based on AUC.

### Methods

Doses: **0, 30, 150, 450 mg/kg/day**  
 Frequency of dosing: Once daily  
 Dose volume: 10 ml/kg  
 Route of administration: Oral gavage  
 Formulation/Vehicle: Sterile water for injection, USP  
 Species/Strain: Rat/ CD[CrI:CD(SD)] from (b) (4)  
 ~10 weeks at dose initiation  
 Number/Sex/Group: 25 females/group; 25 untreated males/group  
 Satellite groups: Toxicokinetics: 3 controls; 6/drug-treated groups  
 TK animals were bled on day 14.  
 Study design: Dosing began 14 days prior to pairing and continued throughout the mating and post-mating period to gestation day (GD) 7. Mated females were euthanized on GD 13.  
 Deviation from study protocol: None that affected study integrity.

### Observations and Results

#### Dose Selection:

Dose selection was based on the results of a dose range-finding study in pregnant rats (Study AT-0313-20). Doses tested were: 50, 150, 450, or 1000 mg/kg/day. A dose of 1000 mg/kg/day produced severe maternal toxicity and lethality after 2 doses. At 450 mg/kg/day, clinical signs of decreased activity and salivation were observed during the dosing period, and decreased food consumption and body weight loss occurred over the first 3 days of treatment which resulted in an overall 18% decrease in body weight gain. A dose of 450 mg/kg/day also produced an increase in post implantation loss. A dose of 50 mg/kg/day produced a transient decrease in maternal body weight gain and

food consumption. Therefore, the 450 mg/kg/day dose was chosen as the high dose for the definitive study.

## Mortality

None

## Clinical Signs

Salivation was observed during the pre mating/mating and gestation periods at 150 and 450 mg/kg/day, with a higher incidence at 450 mg/kg/day (almost all animals).

Completely, or partially, closed eyelids and decreased activity were observed in 18/25 and 21/25 animals, respectively at 450 mg/kg/day during the pre mating/mating phase compared to no observations in any other group including controls. Other findings observed higher in drug-treated animals included lacrimation, discolored and/or sparse hair, and red material around the nose and/or mouth.

Starting on day 9 and continuing through completion of dosing all main-study females and TK animals at 150 and 450 mg/kg/day, were observed cageside for stereotypic behavior approximately 2 to 5 minutes after being returned to the cage following the detailed clinical examination.

Stereotypic behavior including chewing movements, forepaw paddling, freeze, grooming, licking forepaws, and sniffing were observed at 150 and 450 mg/kg/day with increased incidence at 450 mg/kg/day.

Summary of Stereotypy Postdose Premating/Mating Detailed Clinical Observations\* - FEMALE  
Days 9 to 36

Observation	0 mg/kg/day	30 mg/kg/day	150 mg/kg/day	450 mg/kg/day
Number of Animals Alive at Start of Interval	25	25	25	25
<b>Behavior/Activity</b>				
Stereotypy, Chewing movements	0/0	0/0	6/4	22/10
Stereotypy, Forepaw padding	0/0	0/0	35/11	59/18
Stereotypy, Freeze	0/0	0/0	13/8	45/21
Stereotypy, Grooming	0/0	0/0	0/0	2/2
Stereotypy, Licking forepaws	0/0	1/1	0/0	1/1
Stereotypy, Sniffing	0/0	1/1	3/2	10/5

Summary of Stereotypy Postdose Gestation Detailed Clinical Observations\*  
Days 0 to 7

Observation	0 mg/kg/day	30 mg/kg/day	150 mg/kg/day	450 mg/kg/day
Number of Animals Alive at Start of Interval	25	25	23	24
<b>Behavior/Activity</b>				
Stereotypy, Chewing movements	0/0	0/0	36/13	52/19
Stereotypy, Forepaw padding	0/0	0/0	31/11	54/15
Stereotypy, Freeze	0/0	0/0	6/3	15/8
Stereotypy, Licking	0/0	0/0	0/0	1/1
Stereotypy, Licking forepaws	0/0	1/1	0/0	0/0
Stereotypy, Sniffing	0/0	0/0	7/3	5/5

+ Number of times observed/Total number of animals affected

Animals were examined twice daily throughout the study. Detailed clinical exams were conducted daily on main study females, 60-90 min postdose, on GD 13 and for TK animals at 150 and 450 mg/kg/day starting on day 9.

### **Body Weight**

During the pre-mating period, there was a biphasic effect on body weight gain with RDC-0313 treatment indicative of adaptation to the drug. There was an overall statistically significant and dose-dependent, decrease in body weight gain at 30 and 150 mg/kg/day, 23% and 48% compared to controls, respectively. In contrast, there was an overall statistically significant 38% increase in body weight gain at 450 mg/kg/day compared to controls. Although during the first four days of dosing, all dose groups including the high dose group at 450 mg/kg/day either lost weight (150 mg/kg/day) or gained less weight than controls. However thereafter, the high dose group gained more weight than controls. Body weight gain was comparable to controls for all dose groups during the gestation phase, except for a 33% increase in body weight gain at 150 mg/kg/day compared to controls between GD 6 to 10. For most part, the effects on body weight correlated with the effects on food consumption. Body weights were recorded on the day of animal receipt, prior to randomization, on the day of dosing initiation, and twice weekly throughout the study.

### **Food Consumption**

During the first four days of the pre-mating period, there was a dose-related and statistically significant decrease in food consumption at dose levels compared to controls, which correlated with a decrease in body weight gain during the same time period. During the remainder of the pre-mating period, there was a slight decrease in food consumption compared to controls at 30 and 150 mg/kg/day, and both decreases and increases in food consumption at 450 mg/kg/day. During the gestation period, there was a slight increase in food consumption compared to controls at 150 mg/kg/day between GD 10 to 13 and at 450 mg/kg/day between GD 6 to 13. Food consumption was recorded twice weekly up until the mating period, not recorded during mating and then recorded on the same days as body weights were recorded during the gestation period.

### **Toxicokinetics**

Exposure (AUC) to parent RDC-0313 increased greater than dose proportional from 30 to 150 mg/kg/day and almost dose proportional from 150 to 450 mg/kg/day. The elimination half-life ( $t_{1/2}$ ) increased with increasing dose. Exposure (AUC) to metabolite RDC-9986 increased almost dose proportionally while  $C_{max}$  values increased less than dose proportional. Both  $T_{max}$  and  $t_{1/2}$  values for the metabolite increased with increasing dose. Pregnant rats showed 19x higher exposures to parent drug than male rats treated with RDC-0313 at relatively similar doses (150 (F), vs. 100 (M), mg/kg), whereas, the opposite is true for the metabolite at these doses: 2.3x higher in M than F.

TK animals were bled on day 14, from control animals at 1, 6, and 24 hours postdose on and from drug-treated groups at 0.5, 1, 2, 6, 12, and 24 hours postdose

**Table 2. TK Parameters for RDC-0313 on Day 14 Following Repeat Oral Administration of RDC-0313 to Female Rats<sup>a</sup>**

Target Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /Dose (hr*kg*ng/mL/mg)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng/mL/mg)
30	3030	101	1.00	3.15	11,600	387	11,600	387
150	11,200	74.7	2.00	5.41	108,000	720	113,000	754
450	19,900	44.2	2.00	8.24	248,000	551	287,000	637

a. TK parameters were reported to three significant figures.

### Metabolite RDC-9986:

**Table 3. TK Parameters for RDC-9986 on Day 14 Following Repeat Oral Administration of RDC-0313 to Female Rats<sup>a</sup>**

Target Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /Dose (hr*kg*ng/mL/mg)	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng/mL/mg)
30	458	15.3	0.500	4.16	2810	93.7	2860	95.5
150	1190	7.93	2.00	10.7	12,000	80.0	14,900	99.2
450	2550	5.67	6.00	9.64	37,100	82.4	45,800	102

a. TK parameters were reported to three significant figures.

### Dosing Solution Analysis

All dosing formulations were within 99.4% to 101.9% of target RDC-0313 concentrations and were homogeneous.

### Necropsy

There were no drug-related macroscopic findings upon necropsy.

Uterus w/cervix weights (mean absolute and relative to body weight) were statistically significantly increased at 150 mg/kg/day (17% to 20% compared to controls) and at 450 mg/kg/day (30 to 31% compared to controls). Ovary weights were statistically significantly increased at 30 mg/kg/day (14% compared to controls; relative to body weight) and at 450 mg/kg/day (13 to 15% compared to controls; mean absolute and relative to body weight); but no effect was seen at 150 mg/kg/day. The organ weight means were within the historical control ranges for the laboratory and there were no corresponding effects on reproductive and fertility parameters or microscopic findings; therefore, the changes were not considered toxicologically relevant. There were no drug-related microscopic findings in the uterus of any groups.

### Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

The mean cycle length was statistically significantly increased at 450 mg/kg/day, 7.1 days compared to 4.1 days for controls. Eighteen animals at 450 mg/kg/day had prolonged diestrus for 6 to 18 consecutive days during the treatment period. Estrous cycle lengths were not calculated for most of these animals since a complete estrous

cycle was not observed. The mean number of cycles was also significantly decreased at the high dose, 1.7 compared to 2.7 for controls.

There were no drug-related effects on any reproductive or fertility indices. The female mating index was 100%, 96%, and 100% at 30, 150, and 450 mg/kg/day group, respectively, compare to 100% for controls. The female fertility and fecundity indices in all drug-treated groups (84% to 92%) were comparable to controls (92%). Mean copulatory interval ranged from 2.6 to 2.9 days and was comparable across all groups.

Uterine and ovarian examinations:

There were no drug-related effects on any uterine or ovarian parameters including: mean number of corpora lutea, number of implants, number of viable embryos, number of resorptions, and pre- and post-implantation loss.

### 9.2.1 Embryonic Fetal Development: Rat

**Study title:** RDC-0313: An oral study for effects on embryo-fetal developmental toxicity in rats, including a toxicokinetic evaluation

Study no.: AT-0313-22

Study report location: SDN 1

Conducting laboratory and location:  (b) (4)

Date of study initiation: May 24, 2010

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RDC-0313-02 (malate salt form), lot no. 1425-83-1, 96.4%

#### Key Study Findings

- Maternal NOAEL < 25 mg/kg/day due to decreased food consumption and body weight at all doses and increased resorptions and decreased litter size at 300 mg/kg/day.
- Doses  $\geq 100$  mg/kg/day resulted in decreased fetal weights and increased skeletal variations and an increase in total malformations and skeletal malformations at 300 mg/kg/day, which is approximately >248 times the MRHD of 10 mg SAM based on AUC on GD 17.
- Safety margin at fetal NOAEL of 25 mg/kg/day is approximately 29 times the MRHD of 10 mg SAM based on AUC on GD 17.

#### Methods

Doses: **0, 25, 100, 300 mg/kg/day**  
Frequency of dosing: Once daily  
Dose volume: 10 ml/kg  
Route of administration: Oral gavage  
Formulation/Vehicle: Sterile water for injection

Species/Strain: Rat/Crl:CD(SD), time-mated females from  
(b) (4)

Number/Sex/Group: 25/group

Satellite groups: TK: 8/drug-treated groups, 3/control group

Study design: Animals were dosed once daily from gestation day (GD) 6 to 17 at approximately the same time each day.

Deviation from study protocol: None that affected study integrity.

Dose selection was based on the results of a dose range-finding study in pregnant rats (AT-0313-20). RDC-0313 was administered to pregnant rats by oral gavage at dose levels of 50, 150, 450, and 1000 mg/kg/day from GD 6 to 17. The dose of 1000 mg/kg/day produced severe maternal toxicity and lethality. The dose of 450 mg/kg/day resulted in clinical signs of decreased activity and salivation, and decreased food consumption and body weight loss. Post implantation loss was significantly increased at 450 mg/kg/day with corresponding lower mean litter sizes and fetal body weights. Decreased maternal body weight gain and food consumption was observed at the lower doses, but without an effect on post implantation loss or litter size. Therefore, a high dose of 300 mg/kg/day was chosen for the definitive study to produce maternal toxicity without a significant effect on litter sizes for fetal evaluations.

## Observations and Results

### Mortality

None

### Clinical Signs

Dose-dependent salivation was observed in 14/25 and 22/25 animals at 100 and 300 mg/kg/day, respectively compared to no occurrences in any control or low dose animals. Other findings, including sparse hair in different areas, were observed across most dose groups including controls. Detailed clinical exams were conducted on all main study animals daily from GD 6 through 20 at approximately 60-90 minutes post dose.

### Body Weight

During the first few days of dosing between GD 6 to 9, animals at 100 and 300 mg/kg/day lost body weight and animals at 25 mg/kg/day gained significantly less compared to controls. Relative body weight was statistically significantly decreased compared to controls at 100 mg/kg/day during most of the treatment period and statistically significantly decreased compared to controls at 300 mg/kg/day during the entire dosing and post-dosing period. Overall body weight gain during the treatment period (GD 6 to 17) was statistically significantly decreased compared to controls at all dose levels, 12%, 16%, and 27% at 25, 100, and 300 mg/kg/day, respectively. During the post-treatment period between GD 18 to 20, animals at 25 and 100 mg/kg/day gained slightly more weight compared to controls, whereas animals at 300 mg/kg/day still gained significantly less weight compared to controls, indicating no recovery for the

high dose group. The effects on body weight corresponded with decreases in food consumption. Body weights were recorded on GD 0 and daily from GD 6 to 20.

Dose (mg/kg/day)	0	25	100	300
Gestation Body Weight (g) (%) <sup>a</sup>				
GD 7	243.7	-2	-6**	-6**
GD 14	287.3	-3	-5*	-6*
GD 20	359.4	-1	-3	-8**
Gestation Body Weight Change (g) (%) <sup>a</sup>				
GD 6 to 9	12	-62**	-106**	-110**
GD 6 to 18	85	-12**	-16**	-27**
GD 6 to 20	117.7	-5	-9*	-24**

\* = p < 0.05; \*\* = p < 0.01; GD = Gestation Day

<sup>a</sup> - For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). All percent difference values are rounded to the nearest whole number.

[Source: NDA 213378, Toxicology tabulated summary]

### Food Consumption

There was a dose-related and statistically significant decrease in food consumption for all dose groups compared to controls. The decrease in food consumption corresponded to decreases in body weight and body weight gain at similar time points.

Food consumption was recorded on the corresponding body weight days.

Dose (mg/kg/day)	0	25	100	300
Maternal Females (Cont.)				
Food Consumption (g/animal/day) (%) <sup>a</sup>				
GD 6 to 9	24.4	-18**	-26**	-32**
GD 9 to 12	26.6	-8**	-8**	-15**
GD 6 to 18	27.0	-9**	-10**	-13**
GD 6 to 20	27.5	-7**	-9**	-12**

\* = p < 0.05; \*\* = p < 0.01; GD = Gestation Day

<sup>a</sup> - For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). All percent difference values are rounded to the nearest whole number.

[Source: NDA 213378, Toxicology tabulated summary]

### Toxicokinetics

AUC values for RDC-0313 increased greater than dose proportional on both measurement days, whereas  $C_{max}$  values increased almost dose proportional.  $T_{max}$  and  $t_{1/2}$  values increased with increasing dose. There was evidence of a slight increase in exposure after repeat dosing, indicating a small amount of drug accumulation. For metabolite RDC-9986, AUC values increased almost dose proportionally, however  $C_{max}$  values increased much less than dose proportional. Similar to parent drug,  $T_{max}$  and  $t_{1/2}$  values increased over time. There was no evidence of metabolite accumulation.

Blood samples were taken from TK satellite animals for determination of plasma levels of RDC-0313 and its metabolite, RDC-9986. Samples were collected from controls animals at 1, 6, and 24 hrs postdose on GD 6 and 17 and at alternating timepoints from treated TK animals at 0.5, 1, 2, 6, 12, and 24 hrs postdose on GD 6 and 17.

TK Parameters for RDC-0313 on GD 6 Following a Single Oral Administration of RDC-0313 to Female Rats <sup>a,b</sup>								
Dose (mg/kg/day)	Observed	Observed	Observed	Terminal	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /
	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	Elimination Half-Life (hr)		Dose (hr*kg*ng/mL/mg)		Dose (hr*kg*ng/mL/mg)
25	2290	91.6	0.500	1.97	8050	322	8160	327
100	6840	68.4	1.00	2.69	63,800	638	64,000	640
300	19,500	65.0	6.00	5.55	260,000	867	276,000	920

<sup>a</sup>Dose levels were based on content of RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup>TK parameters were reported to three significant figures.

TK Parameters for RDC-9986 on GD 6 Following a Single Oral Administration of RDC-0313 to Female Rats <sup>a,b</sup>								
Dose (mg/kg/day)	Observed	Observed	Observed	Terminal	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /
	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	Elimination Half-Life (hr)		Dose (hr*kg*ng/mL/mg)		Dose (hr*kg*ng/mL/mg)
25	487	19.5	0.500	2.70	2210	88.4	2320	92.9
100	763	7.63	1.00	3.98	7640	76.4	7790	77.9
300	1220	4.07	2.00	NR <sup>c</sup>	19,100	63.7	NR <sup>c</sup>	NR <sup>c</sup>

<sup>a</sup> Dose levels were based on content of RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup> TK parameters were reported to three significant figures.  
<sup>c</sup>Not reported (NR) due to failure of NCA acceptance criteria.

TK Parameters for RDC-0313 on GD 17 Following Repeat Oral Administration of RDC-0313 to Female Rats <sup>a,b</sup>								
Dose (mg/kg/day)	Observed	Observed	Observed	Terminal	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /
	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	Elimination Half-Life (hr)		Dose (hr*kg*ng/mL/mg)		Dose (hr*kg*ng/mL/mg)
25	2100	84.0	1.00	2.61	10,500	420	10,500	420
100	7300	73.0	2.00	3.24	90,100	901	90,900	909
300	19,200	64.0	2.00	7.77	270,000	900	311,000	1040

<sup>a</sup> Dose levels were based on content of RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup>TK parameters were reported to three significant figures.

TK Parameters for RDC-9986 on GD 17 Following Repeat Oral Administration of RDC-0313 to Female Rats <sup>a,b</sup>								
Dose (mg/kg/day)	Observed	Observed	Observed	Terminal	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>last</sub> /	AUC <sub>∞</sub> (hr*ng/mL)	AUC <sub>∞</sub> /
	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	Elimination Half-Life (hr)		Dose (hr*kg*ng/mL/mg)		Dose (hr*kg*ng/mL/mg)
25	440	17.6	0.500	3.19	2620	105	2630	105
100	598	5.98	1.00	4.69	7470	74.7	7740	77.4
300	1230	4.10	6.00	NR <sup>c</sup>	18,700	62.3	NR <sup>c</sup>	NR <sup>c</sup>

<sup>a</sup> Dose levels were based on content of RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup> TK parameters were reported to three significant figures.  
<sup>c</sup>Not reported (NR) due to failure of NCA acceptance criteria.

### Dosing Solution Analysis

Concentrations from samples ranged from 98.5% to 100.2% of nominal. No test article was detected in any control samples.

### Necropsy

There were no drug-related macroscopic findings. Animals were euthanized on GD 20.

### Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There was a statistically significant increase in the percent of post implantation loss at 300 mg/kg/day compared to controls (12.76% compared to 2.29% for controls) and the number of early and late resorptions (1.6 per animal compared to 0.3 per animal for controls). Although it did not reach statistical significance, there was a decrease in the average litter size at 300 mg/kg/day compared to controls (10.0 compared to 11.0) and was outside the historical control range for the laboratory. There were no drug-related effects on pregnancy rates, there were no deaths, abortions, or total resorptions, and no drug-related effects on the number of corpora lutea, implantation sites, viable fetuses, preimplantation loss, or on the fetal sex ratio.

### Offspring (Malformations, Variations, etc.)

There was a statistically significant decrease in fetal weights for males and for males + females combined at both 100 and 300 mg/kg/day compared to controls, and for females at 300 mg/kg/day compared to controls. There was an increase, although not statistically significant, in the overall number of total malformations at 300 mg/kg/day, (0, 0, 1, and 4 fetuses from 0, 0, 1, and 4 litters) from controls, 25, 100, and 300 mg/kg/day groups, respectively. Two of the fetuses had malformations of the forelimbs (bent or misshapen humerus and/or bent radius), hind limbs (bent femur), and bent scapula. These skeletal malformations were not found in the recent historical control dataset for the laboratory. The incidence of malformations at 300 mg/kg/day was 16% greater than controls. There was a statistically significant increase in skeletal variations including bent ribs and non-ossified sternbrae at 300 mg/kg/day compared to controls, and a statistically significant decrease in rudimentary ribs at 100 and 300 mg/kg/day compared to controls, both incidence rates were outside the historical control data. There were no external malformations or variations in any dose group.

		Summary of Fetal Body Weight Values, g				
Endpoint			0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	300 mg/kg/day
Fetal Weight	Males	Mean	4.18 (4.18)	4.13 (4.12)	3.97 (3.97) <sup>a</sup>	3.65 (3.66) <sup>b</sup>
		SD	0.199	0.323	0.263	0.317
		N	24	24	25	25
	Females	Mean	3.95 (3.95)	3.92 (3.92)	3.80 (3.80)	3.50 (3.50) <sup>b</sup>
		SD	0.182	0.274	0.223	0.253
		N	24	24	25	25
	Males + Females	Mean	4.07 (4.07)	4.03 (4.03)	3.89 (3.88) <sup>a</sup>	3.58 (3.59) <sup>b</sup>
		SD	0.166	0.279	0.230	0.251
		N	24	24	25	25

Summary of Individual Fetal Skeletal Observations					
Observation	Classification	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	300 mg/kg/day
No. Litters Evaluated		24	24	25	25
No. Fetuses Evaluated		133	138	139	123
<b>Rib(s)</b>					
Rib(s), Bent	V				
No. Litters(%)		0 (0.0)	1 (4.2)	4 (16.0)	14 (56.0) <sup>b</sup>
No. Fetuses(%) <sup>1</sup>		0 (0.0)	3 (2.2)	8 (5.8)	32 (26.0)
Rib(s), Rudimentary	V				
No. Litters(%)		13 (54.2)	6 (25.0)	5 (20.0) <sup>a</sup>	4 (16.0) <sup>b</sup>
No. Fetuses(%) <sup>1</sup>		22 (16.5)	11 (8.0)	5 (3.6)	9 (7.3)
Rib(s), Smaller than normal	V				
No. Litters(%)		0 (0.0)	0 (0.0)	1 (4.0)	1 (4.0)
No. Fetuses(%) <sup>1</sup>		0 (0.0)	0 (0.0)	3 (2.2)	1 (0.8)

Summary of Individual Fetal Skeletal Observations					
Observation	Classification	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	300 mg/kg/day
No. Litters Evaluated		24	24	25	25
No. Fetuses Evaluated		133	138	139	123
<b>Sternum</b>					
Sternebra(e), Not ossified	V				
No. Litters(%)		13 (54.2)	11 (45.8)	20 (80.0)	24 (96.0) <sup>b</sup>
No. Fetuses(%) <sup>1</sup>		21 (15.8)	24 (17.4)	47 (33.8)	92 (74.8)

No.- Number  
V- Variation

<sup>1</sup>Not statistically analyzed

<sup>a</sup>Significantly different from control; (p<0.05)

<sup>b</sup>Significantly different from control; (p<0.01)

## 9.2.2 Embryonic Fetal Development: Rabbit

**Study title:** RDC-0313: An oral study for effects on embryo-fetal developmental toxicity in rabbits, including a toxicokinetic evaluation

Study no.: AT-0313-23

Study report location: SDN 1

Conducting laboratory and location: (b) (4)

Date of study initiation: June 23, 2010

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RDC-0313-02 (malate salt form), lot no. 1425-83-1, 96.4%

### Key Study Findings

- Maternal toxicity of decreased body weight, body weight gain, and food consumption at all doses, but was considered adverse at 30 and 90 mg/kg/day.
- No drug-related effects on any uterine parameters and no drug-related fetal malformations or variations.
- Maternal NOAEL is 10 mg/kg/day; Fetal NOAEL is 90 mg/kg/day
- Safety margin at embryofetal NOAEL is approximately 143\* times the MRHD of 10 mg SAM based on AUC on GD 19.

\*For calculations of safety margins, mean SAM  $C_{max}$ , and AUC values were corrected for RDC-1066 interference on SAM concentrations (ie.,  $C_{max}$  values were reduced by 30%, 23%, and 21% for the 10, 30, and 90 mg/kg/day group, respectively, and AUC values were reduced by 26%, 24%, and 16% for the 10, 30, and 90 mg/kg/day groups, respectively) based on results from the "RDC-1066 Cross-Assay Interference Nonclinical Evaluation Summary" report (see pharmacokinetic section of review for details). Therefore, the AUC value at the embryofetal NOAEL of 90 mg/kg/day was corrected to 52,248 ng.hr/ml from the original value of 62,200 ng.hr/ml.

## Methods

Doses:	<b>0, 10, 30, 90 mg/kg/day</b>
Frequency of dosing:	Once daily
Dose volume:	5 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water for injection
Species/Strain:	Rabbit/New Zealand white (time-mated females) ~ 7.5 months old from [REDACTED] (b) (4)
Number/Sex/Group:	23/group
Satellite groups:	TK: 5/drug-treated group, 3/control group
Study design:	Animals were dosed once daily from gestation day (GD) 7-19 and euthanized on GD 29. Uterine contents were examined, and all fetuses were examined.
Deviation from study protocol:	None that affected study integrity.

Dose selection was based on the results of a dose range-finding study in rabbits (AT-0313-21). In the first part of that study, the dose tolerance phase, non-pregnant rabbits were administered RDC-0313 by oral gavage at dose levels of 2, 10, 20, or 200 mg/kg/day for 7 days. The 200 mg/kg/day dose resulted in mortality and marked reduction in food consumption and body weight. In the second part of the study, time-mated female rabbits were administered RDC-0313 by oral gavage at doses of 3, 10, 30, or 100 mg/kg/day from GD 7 through GD 19. In this phase, the 100 mg/kg/day dose produced a severe decrease in food consumption and body weight, and at termination there was one dead litter and reduced numbers of live fetuses in the remaining litters. There were minimal effects on maternal food consumption at the other doses levels and no effects on uterine or fetal parameters. Therefore, 90 mg/kg/day was chosen as the high dose for the definitive study.

## Observations and Results

### Mortality

No pregnant animals died during the study.

### **Clinical Signs**

3 females at 90 mg/kg/day aborted on GDs 18, 23, and 25, and 1 female at 90 mg/kg/day delivered early on GD 28. The female that aborted on GD 18 had few/absent feces and low food consumption on GD 16, and the uterus had total litter resorption. On the days preceding the abortions or early delivery of the other 3 females, they all were observed with few/absent feces and thinness for several days, and markedly reduced food intake for at least 10 days prior to the event. These 3 females had several live fetuses or normally developing implants. There were no abortions in any control or 10 or 30 mg/kg/day females, therefore the abortions and early delivery at 90 mg/kg/day were considered drug-related. All other main study and TK animals survived to scheduled necropsy.

Few/absent feces were observed in animals from all groups including controls; however, there was a drug-related increase in the number of animals with the finding at 30 and 90 mg/kg/day compared to controls. This finding may be due to the pharmacology of the drug being an opioid partial agonist at kappa and delta receptors, and its metabolite is an opioid agonist. 7 females at 90 mg/kg/day also had a thin appearance during the last week of the study. These clinical signs correlated with decreased food consumption at 90 mg/kg/day. Three animals at 90 mg/kg/day had red material in the pan/bedding which correlated with abortion of early delivery in these animals.

All animals were observed for morbidity, mortality, injury, and availability of food and water twice daily. Detailed clinical examinations, conducted outside the cage, were conducted on each main study animal daily between GD 7 to GD 29, 60 to 90 minutes post-dose on dosing days.

### **Body Weight**

Animals at 90 mg/kg/day lost weight during the dosing period from GD 7 to 19, which was statistically significantly decreased, 154% compared to controls. Animals at 10 and 30 mg/kg/day lost weight during GD 7 to 10, but only animals at 30 mg/kg/day had a statistically significant decrease in body weight gain of 71% compared to controls over the entire dosing period (GD 7 to 19). Relative body weight at the end of the dosing period on GD 19 was 2%, 6%, and 8% decreased compared to controls at 10, 30, and 90 mg/kg/day, respectively. Body weights at 90 mg/kg/day remained statistically significantly lower than controls during the post-treatment period. The significant increase in body weight gain during the post-treatment period at 90 mg/kg/day was primarily due to the exclusion of animals that aborted or delivered early. The statistically significant decrease in relative body weight and body weight gain at 30 and 90 mg/kg/day correlated with a decrease in food consumption and was considered adverse. Body weights for all animals were measured and recorded on GD 0, daily from GD 7-19, and on GD 21, 23, 25, 27, and 29.

Daily Dose (mg/kg/day)	0	10	30	90
Gestation Body Weight (kg) (%) <sup>e</sup>				
GD 10	3.559	-3	-6**	-6**
GD 13	3.628	-3	-6**	-7**
GD 16	3.691	-3	-6*	-8**
GD 19	3.741	-2	-6*	-8**
Gestation Body Weight Change (kg)				
GD 7-10	0.021	-0.068**	-0.112**	-0.197**
GD 10-13	0.070	0.073	0.059	0.028
GD 13-16	0.063	0.068	0.070	0.039
GD 16-19	0.050	0.059	0.041	0.025
Gestation Food Consumption (g/animal/day) (%) <sup>e</sup>				
GD 7-10	157.4	-40**	-51**	-69**
GD 10-13	141.5	-22**	-33**	-56**
GD 13-16	134.9	-16	-34**	-51**
GD 16-19	141.7	-1	-17	-40**

GD = Gestation Day; \* = p<0.05; \*\* = p<0.01

e - For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). All percent difference values are rounded to the nearest whole number.

[Source: NDA 213378, Toxicology tabulated summary]

### Food Consumption

Food consumption was statistically significantly decreased across all dose groups compared to controls. The greatest decrease was seen between GD 7 to 10 of 40%, 51%, and 69% compared to controls, respectively at 10, 30, and 90 mg/kg/day. Food consumption during the entire dosing period from GD 7 to 19 was also statistically significantly decreased across all dose groups, 20%, 34%, and 55% compared to controls, respectively at 10, 30, and 90 mg/kg/day. Food consumption was comparable to controls for all dose groups during the post-treatment period on GD 19 to 29. The decrease in food consumption was considered adverse and correlated with an overall decrease in relative body weight and body weight gain at 30 and 90 mg/kg/day, and at 10 mg/kg/day only during GD 7 to 10. Food consumption for main-study animals was recorded daily and reported on the corresponding body weight days.

### Toxicokinetics

AUC values for RDC-0313 increased greater than dose-proportional, but C<sub>max</sub> values increased almost dose-proportionally. There was some evidence of drug accumulation of RDC-0313 after repeat dosing of the 30 and 90 mg/kg/day dose. The T<sub>max</sub> values of metabolite RDC-9986 were comparable to those for the parent drug, indicating a rapid conversion in vivo. Exposure (AUC) to the metabolite increased slightly greater than dose-proportional, but there was no evidence of any accumulation of the metabolite after repeat dosing of RDC-0313. The elimination half-life for RDC-0313 and metabolite RDC-9986 increased slightly with increasing dose on GD 19.

Blood samples were collected from TK animals via the jugular vein for determination of the plasma concentrations of RDC-0313 and its metabolite, RDC-99864. Samples were collected from control TK animals at 1, 6, and 24 hours postdose on GD 7 and 19, and from treated TK animals at 0.5, 1, 2, 6, 12, and 24 hours postdose on GD 7 and 19.

Mean TK Parameters for RDC-0313 on GD 7 Following a Single Oral Administration of RDC-0313 to Female Rabbits <sup>a</sup>								
Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/ mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng /mL)	AUC <sub>last</sub> / Dose (hr*kg*ng /mL/mg)	AUC <sub>∞</sub> (hr*ng /mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng /mL/mg)
10	831	83.1	0.500 <sup>b</sup>	1.69	2310	231	2320	232
30	3200	107	1.00 <sup>b</sup>	2.54	9380	313	9390	313
90	12,100	134	0.500 <sup>b</sup>	2.47	43,100	479	43,100	479

<sup>a</sup>TK parameters were reported to three significant figures. RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup>Represents the median.

Mean TK Parameters for RDC-9986 on GD 7 Following a Single Oral Administration of RDC-0313 to Female Rabbits <sup>a</sup>								
Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/ mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng /mL)	AUC <sub>last</sub> / Dose (hr*kg*ng /mL/mg)	AUC <sub>∞</sub> (hr*ng /mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng /mL/mg)
10	315	31.5	0.500 <sup>b</sup>	3.57	1080	108	1090	109
30	1310	43.8	0.500 <sup>b</sup>	3.64	4570	152	4590	153
90	3970	44.1	0.500 <sup>b</sup>	3.12	18,700	208	18,800	209

<sup>a</sup>TK parameters were reported to three significant figures. RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup>Represents the median.

Mean TK Parameters for RDC-0313 on GD 19 Following Repeat Oral Administration of RDC-0313 to Female Rabbits <sup>a</sup>								
Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/ mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng /mL)	AUC <sub>last</sub> / Dose (hr*kg*ng /mL/mg)	AUC <sub>∞</sub> (hr*ng /mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng /mL/mg)
10	797	79.7	0.500 <sup>b</sup>	1.99	2170	217	2180	218
30	3430	114	1.00 <sup>b</sup>	2.39	11,400	380	11,400	380
90	10,700	119	1.00 <sup>b</sup>	3.76	62,200	691	63,600	707

<sup>a</sup>TK parameters were reported to three significant figures. RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup>Represents the median.

Mean TK Parameters for RDC-9986 on GD 19 Following Repeat Oral Administration of RDC-0313 to Female Rabbits <sup>a</sup>								
Dose (mg/kg/day)	Observed C <sub>max</sub> (ng/mL)	Observed C <sub>max</sub> /Dose (kg*ng/ mL/mg)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	AUC <sub>last</sub> (hr*ng /mL)	AUC <sub>last</sub> / Dose (hr*kg*ng /mL/mg)	AUC <sub>∞</sub> (hr*ng /mL)	AUC <sub>∞</sub> /Dose (hr*kg*ng /mL/mg)
10	251	25.1	0.500 <sup>b</sup>	3.44	789	78.9	799	79.9
30	1350	45.0	1.00 <sup>b</sup>	3.77	4740	158	4770	159
90	2820	31.4	2.00 <sup>b</sup>	4.50	19000	211	19,600	218

<sup>a</sup>TK parameters were reported to three significant figures. RDC-0313 administered as the malate salt, RDC-0313-02.  
<sup>b</sup>Represents the median.

### Dosing Solution Analysis

All dosing formulations analyzed were 99.3% to 101.9% of nominal and were homogenous. No test article was found in any of the analyzed control samples.

### Necropsy

All animals, except two control females, were pregnant. Three females at 90 mg/kg/day had abortions on GDs 18, 23, and 25, and 1 female at 90 mg/kg/day delivered early on GD 28. There were no drug-related macroscopic findings upon necropsy.

### Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no drug-related effects on any uterine parameters (number of corpora lutea, implantation sites, viable fetuses, litter size, resorptions, pre- and post-implantation loss, and fetal sex ratio). At terminal necropsy, there were 21, 23, 23, and 19 live litters for fetal evaluation from the control, 10, 30, and 90 mg/kg/day, respectively. There were no drug-related effects on fetal body weights.

### Offspring (Malformations, Variations, etc.)

The overall incidence of litters and fetuses with malformations (external, visceral, and skeletal) was similar across all groups including controls, and there were no statistically significant changes. One fetus had an omphalocele external malformation but was within the historical control range and therefore not considered drug-related. There were a few visceral and skeletal malformations and variations observed across all dose groups including controls, but none of the findings were considered drug-related due to the findings also being observed in controls, and the incidence rates within the historical control ranges for the laboratory.

### 9.2.3 Embryonic Fetal Development: Rat combination SAM/OLZ

**Study Title:** RDC-0313-02 and Olanzapine: An Oral Study for Effects on Embryo- Fetal Development in Rats with a Toxicokinetic Evaluation

Study no.:	AT-0313-45
Study report location:	EDR SDN 196
Conducting laboratory and location:	 (b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Samidorphan (RDC-0313-02; malate salt), Alkermes lot no. 0000082573, 98.9%. Olanzapine, Alkermes lot no. 0000081227, 99.8%.

#### Methods

Doses:	0/0, 10/0.5, 50/2, 200/6, 200/0 RDC-0313/Olanzapine mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	25 time-mated females/group
Dose volume:	5 ml/kg for each test article
Formulation/Vehicle:	Sterile water for injection for RDC-0313 and 50 mM citrate buffer in sterile water for injection, pH 4 for olanzapine
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	Sprague-Dawley
Comment on Study Design and Conduct:	Animals were dosed from gestation day (GD) 6 through 17 and sacrificed on GD 20.
Dosing Solution Analysis:	Concentrations of RDC-0313 and olanzapine were within the acceptable range ( $\leq 10\%$ of nominal concentrations) for all formulations and ranged between 100.2% to 102.3% for RDC-0313 and 94.9% to 100.6% for olanzapine.

#### Basis of dose selection:

A preliminary pilot prenatal development study (study AT-0313-44) with toxicokinetic analysis was conducted in rats. Time-mated pregnant Sprague-Dawley rats were orally administered RDC-0313/olanzapine at dose levels of 0/0, 0/8, 300/0, 10/0.5, 30/2, 100/4, 300/8 mg/kg/day. Clinical signs were observed with all drug groups (see Sponsor's table below). On GD 18, group mean body weights were approximately 8%, 5%, 5%, 5%, 8%, and 20% lower than mean control values in the 0/8, 300/0, 10/0.5, 30/2, 100/4, and 300/8 mg/kg/day RDC-0313/olanzapine groups, respectively and correlated with decreased food consumption. A decrease in the number of live fetuses and fetal body weights were observed at 0/8, 300/0, and 300/8 mg/kg/day RDC-0313/olanzapine. Based on clinical signs and a >10% decreases in body weight at 300/8 mg/kg/day, this dose was deemed too high for the definitive study; therefore, a high dose of 200/6 mg/kg/day RDC-0313/olanzapine was selected for the definitive study. An olanzapine-alone group was not included in the definitive study.

<b>RDC-0313/olanzapine Clinical observations</b>	<b>0/0 mg/kg/ day</b>	<b>0/8 mg/kg/ day</b>	<b>300/0 mg/kg/ day</b>	<b>10/0.5 mg/kg/ day</b>	<b>30/2 mg/kg/ day</b>	<b>100/4 mg/kg/ day</b>	<b>300/8 mg/kg/ day</b>
Decreased Activity	0/0	33/4	0/0	0/0	1/1	41/5	58/5
Salivation	0/0	0/0	21/5	0/0	0/0	0/0	2/2
Vocalization	0/0	8/2	0/0	0/0	0/0	0/0	0/0
Shallow Breathing	0/0	0/0	0/0	0/0	0/0	0/0	8/3
Lacrimation	0/0	6/2	0/0	0/0	0/0	9/4	17/5
Thin	0/0	0/0	0/0	0/0	0/0	0/0	33/5
Eyes Partially Closed	0/0	35/5	0/0	0/0	0/0	2/1	33/5
Pupils Dilated	0/0	35/5	0/0	0/0	4/1	8/1	25/5
Splayed Limbs	0/0	0/0	0/0	0/0	0/0	0/0	9/3
Impaired Limb Function	0/0	0/0	0/0	0/0	0/0	0/0	15/4
Brown/Red Discharge (Vulva)	0/0	4/3	1/1	2/2	4/4	5/4	5/4

Data presented as number of times observed/number of animals (5 animals observed per group)

[Source: study report AT-0313-44]

Reviewer's note: Because an olanzapine-alone group was not included in the definitive study, direct comparisons to olanzapine cannot be made. However, an olanzapine-alone group was included in the preliminary pilot study described above, therefore toxicity related to olanzapine may be inferred based on data from the preliminary study in addition to toxicity described in the approved label for olanzapine (see appendix).

#### **Key Study Findings:**

- Maternal toxicity was observed at all dose levels which included decreased body weight and food consumption. Maternal NOAEL not determined.

- Reduced mean fetal body weights at 200/6 and 200/0 mg/kg/day SAM/OLZ. Increased resorptions and post-implantation loss, with correlating lower mean viable fetuses and litter size, were observed at 200/6 mg/kg/day.
- An increase in bent scapula, bent ribs, and fetuses with sternebra(e) not ossified at 200/6 mg/kg/day and 200/0 mg/kg/day SAM/OLZ, which is approximately 6 and 448 times the MRHD of 20/10 mg OLZ/SAM based on AUC, respectively for OLZ and SAM.
- Embryofetal NOAEL is 50/2 mg/kg/day SAM/OLZ, which is approximately 80 and 0.9 times the MRHD of 20/10 mg OLZ/SAM based on AUC, respectively.

## **Observations and Results**

### **F<sub>0</sub> Dams**

#### **Mortality**

One RDC-0313 alone TK animal was found dead on GD 14; macroscopic findings, findings including yellow fluid in the thoracic cavity, white discoloration and moderately firm lung lobe, suggest possible gavage-related trauma.

#### **Clinical Signs**

Detailed clinical exams were conducted daily from GD 6 through GD 20. Exams were conducted 45 minutes postdose on GD 6 and then 4 hours postdose (due to clinical signs being observed around this time) from GD 7 through 20.

Many clinical signs (decreased activity, lacrimation, partially closed eyes, and brown/red discharge) are most likely attributed to olanzapine, based on similar findings in the olanzapine alone group from the preliminary study (study AT-0313-44). In contrast, salivation and scabbed areas are most likely attributed to RDC-0313. Red material around the eye/nose and tremors were only observed in the RDC-0313/olanzapine combined groups.

<b>Table O. Treatment-Related Clinical Observations</b>					
<b>RDC-0313/olanzapine Clinical Observations</b>	<b>0/0 mg/kg/day</b>	<b>10/0.5 mg/kg/day</b>	<b>50/2 mg/kg/day</b>	<b>200/6 mg/kg/day</b>	<b>200/0 mg/kg/day</b>
Decreased Activity	0/0	0/0	2/2	207/25	6/2
Salivation	0/0	0/0	1/1	3/3	36/10
Lacrimation	0/0	0/0	1/1	13/7	0/0
Eyes Partially Closed	0/0	0/0	1/1	123/18	0/0
Red Material around eyes/nose	0/0	2/2	1/1	15/8	0/0
Scabbed Areas (Cervical Region)	3/1	1/1	0/0	29/4	6/1
Red Material on the face	0/0	0/0	0/0	14/7	0/0
Hunched Posture	0/0	0/0	0/0	67/12	0/0
Thin	0/0	0/0	0/0	17/3	0/0
Brown/Red Discharge (Vulva)	0/0	0/0	1/1	12/8	1/1
Tremors	0/0	0/0	0/0	3/2	0/0
Teeth discolored white	0/0	9/1	35/3	4/1	0/0
Number of times observed/Total number of animals affected					

### Body Weight

There was a statistically significant decrease in mean body weight at 50/2 and 200/6 mg/kg/day (RDC-0313/olanzapine) compared to controls during the entire study from GD 6 to 20 and at 200/0 mg/kg/day from GD 18 to 20, but to a lesser degree. The addition of olanzapine in the 200/6 mg/kg/day group caused a greater decrease in body weight compared to the RDC-0313 alone group (200/0 mg/kg/day). The greatest decrease in body weight gain occurred from GD 6 to 9 in all dose groups and included body weight loss in the 200/6 mg/kg/day group only. There was a 13%, 21%, 50%, and 15% decrease in body weight gain during the dosing period from GD 6 to 18, and all groups were statistically significantly different from controls; and the 200/6 mg/kg/day group was also statistically significantly different from the RDC-0313 alone group (200/0 mg/kg/day). The effects on body weight correlated with decreases in food consumption. Body weights were recorded on GD 6, 9, 12, 15, 18, and 20.

Interval	0/0 mg/kg/day	10/0.5 mg/kg/day	50/2 mg/kg/day	200/6 mg/kg/day	200/0 mg/kg/day
GD 9	251.3	244.3	238.2 <sup>a</sup>	216.8 <sup>a,b</sup>	240.8
GD 12	274.2	262.8	255.9 <sup>a</sup>	240.3 <sup>a,b</sup>	264.0
GD 15	292.7	281.6	276.8 <sup>a</sup>	262.9 <sup>a,b</sup>	285.8
GD 18	332.5	320.2	312.0 <sup>a</sup>	286.6 <sup>a,b</sup>	317.2 <sup>a</sup>
GD 20	367.3	357.0	345.4 <sup>a</sup>	311.6 <sup>a,b</sup>	349.4 <sup>a</sup>

<sup>a</sup>statistically significant from 0/0 mg/kg/day  
<sup>b</sup>statistically significant from 200/0 mg/kg/day

Interval	0/0 mg/kg/day	10/0.5 mg/kg/day	50/2 mg/kg/day	200/6 mg/kg/day	200/0 mg/kg/day
GD 6-9	14.4	7.4 <sup>a</sup>	1.8 <sup>a</sup>	-21.8 <sup>a,b</sup>	5.1 <sup>a</sup>
GD 9-12	22.9	18.6	17.8 <sup>a</sup>	23.5	23.2
GD 12-15	18.5	18.7	20.9	22.6	21.7
GD 15-18	39.8	38.6	35.2	23.7 <sup>a,b</sup>	31.4 <sup>a</sup>
GD 18-20	34.8	36.8	33.3	25.0 <sup>a,b</sup>	32.2
GD 6-18	95.6	83.2 <sup>a</sup>	75.7 <sup>a</sup>	48.0 <sup>a,b</sup>	81.4 <sup>a</sup>
GD 6-20	130.5	120.0 <sup>a</sup>	109.0 <sup>a</sup>	73.0 <sup>a,b</sup>	113.6 <sup>a</sup>

<sup>a</sup>Statistically significant from 0/0 mg/kg/day group  
<sup>b</sup>Statistically significant from 200/0 mg/kg/day group

### Food Consumption

Food consumption was recorded on the same days as body weight recordings. Food consumption was statistically significantly decreased in all dose groups compared to controls during the first few days of dosing from GD 6 to 12. The greatest decrease in food consumption occurred at 200/6 mg/kg/day from GD 12 to 15 compared to controls.

The addition of olanzapine to 200 mg/kg/day RDC-0313 (200/6 mg/kg/day) caused a greater decrease in food consumption than RDC-0313 alone (200/0 mg/kg/day).

### Cesarean Section Data

All main study animals were pregnant; only one TK female at 50/2 mg/kg/day was not pregnant. At the high combination dose of 200/6 mg/kg/day, there were statistically significant changes compared to controls including a decrease in the mean number of viable fetuses per animal and average litter size per animal, an increase in post-implantation loss, and an increase in the mean number of total resorptions (both early and late resorptions). There were no statistically significant changes in the RDC-0313 alone group (200/0 mg/kg/day) compared to controls. However, in the rat embryofetal development study with RDC-0313 alone (study AT-0313-22), there was a statistically significant increase in post-implantation loss and both early and late resorptions compared to controls at a higher dose of 300 mg/kg/day. An olanzapine-alone treatment group was not included in the current study; although, effects on post-implantation loss and total resorptions were not observed with the olanzapine treatment alone (8 mg/kg/day) in the preliminary study (study AT-0313-44). However, increases in the number of early resorptions was reported in rats treated with higher doses of olanzapine (18 mg/kg/day) from an embryofetal development study described in the approved label for olanzapine (Zyprexa) (see appendix). Therefore, the increase in post-implantation loss and total resorptions observed in the present study are most likely due to the high dose combination of both RDC-0313 and olanzapine.

Parameter	0/0 mg/kg/day	10/0.5 mg/kg/day	50/2 mg/kg/day	200/6 mg/kg/day	200/0 mg/kg/day
Mean number of viable fetuses	13.2	12.9	12.3	10.6 <sup>a</sup>	12.6
% post-implantation loss	2.89	3.65	3.68	14.59 <sup>a</sup>	5.23
Litter Size per Animal	13.2	12.9	12.3	10.6 <sup>a</sup>	12.6
Mean number of resorptions (total)	0.4	0.5	0.5	1.7 <sup>a</sup>	0.7

<sup>a</sup>Statistically significant from 0/0 mg/kg/day group

### Necropsy/ Histopathology

There were no drug-related macroscopic findings in dams from any dose group.

### Toxicokinetics

Blood samples were collected from TK satellite animals at 0.5 and 2 hours postdose from control animals and at 0.5, 1, 2, 6, 12, and 24 hours postdose from treated animals on GD 6 and 17. Plasma concentrations of olanzapine, RDC-0313 and its metabolites (RDC-9986 and RDC-1066) were measured.

The addition of 6 mg/kg olanzapine to 200 mg/kg RDC-0313 did not significantly affect the exposure (AUC) of olanzapine, or metabolites RDC-9986 and RDC-1066 compared to the exposure of each produced in the 200 mg/kg RDC-0313 alone group. The half-life ( $t_{1/2}$ ) value of RDC-0313 increased with increasing dose of the combination, from approximately 2 hours to 8 hours; however, the addition of 6 mg/kg olanzapine to 200 mg/kg did not significantly affect the half-life of RDC-0313. The half-lives for metabolites

RDC-9986 and RDC-1066 increased with increasing dose of the combination, from approximately 2 hours to 15 and 24 hours. The addition of 6 mg/kg olanzapine to 200 mg/kg RDC-0313 appears to increase the half-life for metabolites RDC-9986 and RDC-1066 compared to the half-life values of the metabolites in the 200 mg/kg RDC-0313 alone treated groups. However, the data were variable amongst all groups.

**Table 1: RDC-0313 Toxicokinetic Parameters on GD 6 and GD 17 Following Oral Gavage Administration of 10/0.5 mg/kg RDC-0313/Olanzapine (Group 7), 50/2 mg/kg RDC-0313/Olanzapine (Group 8), 200/6 mg/kg RDC-0313/Olanzapine (Group 9), or 200/0 mg/kg RDC-0313/Olanzapine (Group 10) to Female Rats**

Analyte	Group	Dose Level (RDC-0313/Olanzapine) (mg/kg)	GD	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	R <sup>2</sup>	T <sub>1/2</sub> (hr)	Group 9:Group 10 Ratio <sup>c</sup>
RDC-0313	7	10/0.5	6	709	70.9	0.5	12	2520	2560	256	NA	1.59	NA
RDC-0313	7	10/0.5	17	812	81.2	1	12	3470	3580	358	1.40	2.00	NA
RDC-0313	8	50/2	6	4540	90.7	1	12	25400	29300	586	NA	3.86	NA
RDC-0313	8	50/2	17	3470	69.3	0.5	24	29200	29200	584	0.996	2.70	NA
RDC-0313	9	200/6	6	13100	65.5	2	24	141000	141000	707	NA	8.55	0.966
RDC-0313	9	200/6	17	15200	76.2	0.5	24	163000	163000	816	1.15	6.21	0.791
RDC-0313	10	200/0	6	13000	64.8	0.5	24	146000	146000	732	NA	7.55	NA
RDC-0313	10	200/0	17	14700	73.5	6	24	206000	206000	1030	1.41	NA <sup>b</sup>	NA

NA - Not applicable  
a: R = AUC<sub>0-24hr</sub> GD 17 / AUC<sub>0-24hr</sub> GD 6  
b: T<sub>1/2</sub> not determined due to insufficient plasma concentration data  
c: Group 9:Group 10 Ratio = AUC<sub>0-24hr</sub> Group 9 / AUC<sub>0-24hr</sub> Group 10

**Table 2: RDC-9986 Toxicokinetic Parameters on GD 6 and GD 17 Following Oral Gavage Administration of 10/0.5 mg/kg RDC-0313/Olanzapine (Group 7), 50/2 mg/kg RDC-0313/Olanzapine (Group 8), 200/6 mg/kg RDC-0313/Olanzapine (Group 9), or 200/0 mg/kg RDC-0313/Olanzapine (Group 10) to Female Rats**

Analyte	Group	Dose Level (RDC-0313/Olanzapine) (mg/kg)	GD	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	R <sup>2</sup>	M:P <sup>b</sup>	T <sub>1/2</sub> (hr)	Group 9:Group 10 Ratio <sup>d</sup>
RDC-9986	7	10/0.5	6	310	31.0	0.5	12	1220	1290	129	NA	0.502	2.41	NA
RDC-9986	7	10/0.5	17	223	22.3	0.5	12	1080	1160	116	0.900	0.323	2.74	NA
RDC-9986	8	50/2	6	799	16.0	2	24	6670	6670	133	NA	0.228	2.32	NA
RDC-9986	8	50/2	17	410	8.19	2	24	4340	4340	86.8	0.651	0.149	3.75	NA
RDC-9986	9	200/6	6	1360	6.78	2	24	16700	16700	83.5	NA	0.118	NA <sup>c</sup>	0.865
RDC-9986	9	200/6	17	823	4.12	0.5	24	11500	11500	57.4	0.687	0.0703	15.2	0.596
RDC-9986	10	200/0	6	1520	7.60	0.5	24	19300	19300	96.6	NA	0.132	12.0	NA
RDC-9986	10	200/0	17	1510	7.57	1	24	19300	19300	96.6	1.00	0.0938	5.13	NA

NA - Not applicable  
a: R = AUC<sub>0-24hr</sub> GD 17 / AUC<sub>0-24hr</sub> GD 6  
b: RDC-9986:RDC-0313 Ratio = AUC<sub>0-24hr</sub> RDC-9986 / AUC<sub>0-24hr</sub> RDC-0313  
c: T<sub>1/2</sub> not reported due to an adjusted R<sup>2</sup> less than 0.9  
d: Group 9:Group 10 Ratio = AUC<sub>0-24hr</sub> Group 9 / AUC<sub>0-24hr</sub> Group 10

**Table 3: RDC-1066 Toxicokinetic Parameters on GD 6 and GD 17 Following Oral Gavage Administration of 10/0.5 mg/kg RDC-0313/Olanzapine (Group 7), 50/2 mg/kg RDC-0313/Olanzapine (Group 8), 200/6 mg/kg RDC-0313/Olanzapine (Group 9), or 200/0 mg/kg RDC-0313/Olanzapine (Group 10) to Female Rats**

Analyte	Group	Dose Level (RDC-0313/Olanzapine) (mg/kg)	GD	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	R <sup>2</sup>	M.P <sup>b</sup>	T <sub>1/2</sub> (hr)	Group 9:Group 10 Ratio <sup>d</sup>
RDC-1066	7	10/0.5	6	15.8	1.58	0.5	6	47.8	54.5	5.45	NA	0.0213	2.03	NA
RDC-1066	7	10/0.5	17	16.4	1.64	0.5	12	77.7	79.8	7.98	1.46	0.0223	2.00	NA
RDC-1066	8	50/2	6	33.2	0.663	1	12	204	234	4.67	NA	0.00797	4.08	NA
RDC-1066	8	50/2	17	30.3	0.606	1	24	295	295	5.90	1.26	0.0101	2.80	NA
RDC-1066	9	200/6	6	70.1	0.350	0.5	24	666	666	3.33	NA	0.00471	24.6	0.953
RDC-1066	9	200/6	17	74.9	0.375	0.5	24	782	782	3.91	1.17	0.00479	15.4	0.811
RDC-1066	10	200/0	6	62.3	0.311	0.5	24	699	699	3.49	NA	0.00477	NA <sup>c</sup>	NA
RDC-1066	10	200/0	17	77.4	0.387	2	24	964	964	4.82	1.38	0.00468	7.01	NA

NA - Not applicable  
a: R = AUC<sub>0-24hr</sub> GD 17/AUC<sub>0-24hr</sub> GD 6  
b: RDC-1066:RDC-0313 Ratio = AUC<sub>0-24hr</sub> RDC-1066/AUC<sub>0-24hr</sub> RDC-0313  
c: T<sub>1/2</sub> not reported due to an adjusted R<sup>2</sup> less than 0.9  
d: Group 9:Group 10 Ratio = AUC<sub>0-24hr</sub> Group 9/AUC<sub>0-24hr</sub> Group 10

**Table 4: Olanzapine Toxicokinetic Parameters on GD 6 and GD 17 Following Oral Gavage Administration of 10/0.5 mg/kg RDC-0313/Olanzapine (Group 7), 50/2 mg/kg RDC-0313/Olanzapine (Group 8), and 200/6 mg/kg RDC-0313/Olanzapine (Group 9) to Female Rats**

Analyte	Group	Dose Level (RDC-0313/Olanzapine) (mg/kg)	GD	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (kg*ng/mL/mg)	T <sub>max</sub> (hr)	T <sub>last</sub> (hr)	AUC <sub>Tlast</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> (hr*ng/mL)	AUC <sub>0-24hr</sub> /Dose (hr*kg*ng/mL/mg)	R <sup>2</sup>	T <sub>1/2</sub> (hr)
Olanzapine	7	10/0.5	6	11.6	23.2	0.5	6	33.2	37.0	74.0	NA	1.63
Olanzapine	7	10/0.5	17	23.4	46.8	1	6	65.4	74.6	149	2.02	NA <sup>b</sup>
Olanzapine	8	50/2	6	95.7	47.9	1	12	566	677	339	NA	4.84
Olanzapine	8	50/2	17	121	60.5	0.5	24	959	959	480	1.42	2.76
Olanzapine	9	200/6	6	345	57.5	2	24	3300	3300	550	NA	NA <sup>c</sup>
Olanzapine	9	200/6	17	661	110	0.5	24	6000	6000	1000	1.82	9.99

NA - Not applicable  
a: R = AUC<sub>0-24hr</sub> Day GD 17/AUC<sub>0-24hr</sub> Day GD 6  
b: T<sub>1/2</sub> not determined due to insufficient plasma concentration data  
c: T<sub>1/2</sub> not determined due to an adjusted R<sup>2</sup> value less than 0.9

## F<sub>1</sub> Offspring

### Terminal Observations

There was a statistically significant decrease in mean fetal body weight for males, females, and both sexes combined at 200/6 and 200/0 mg/kg/day compared to controls. The decrease was slightly greater for the RDC-0313/olanzapine (200/6 mg/kg/day) combined group compared to the RDC-0313 alone group (200/0 mg/kg/day) suggesting an additive effect on fetal body weights with both RDC-0313 and olanzapine. A decrease in fetal body weights was also observed in the preliminary pilot prenatal development study at a dose of 8 mg/kg/day olanzapine alone (study AT-0313-44).

Table T. Mean Fetal Body Weights (g)					
	0/0 mg/kg/day	10/0.5 mg/kg/day	50/2 mg/kg/day	200/6 mg/kg/day	200/0 mg/kg/day
Males	4.25 (4.27)	4.13 (4.14)	4.11 (4.11)	3.75 (3.70) <sup>a</sup>	3.89 (3.90) <sup>a</sup>
Females	4.04 (4.06)	3.96 (3.97)	3.87 (3.87)	3.54 (3.51) <sup>a</sup>	3.69 (3.70) <sup>a</sup>
Sexes Combined	4.15 (4.18)	4.05 (4.06)	4.01 (4.00)	3.63 (3.59) <sup>a,b</sup>	3.79 (3.80) <sup>a</sup>
<sup>a</sup> Mean statistically significant from 0/0 mg/kg/day group					
<sup>b</sup> Mean statistically significant from 200/0 mg/kg/day group					
()- Least Square Mean					

### Fetal Malformations/ Variations (external, visceral, skeletal)

Drug-related skeletal malformations and variations were observed in fetuses from RDC-0313 treated groups. There were no drug-related external or visceral fetal malformations or variations. External malformations were observed in two fetuses from the 200 mg/kg/day RDC-0313 alone group which included one fetus with microphthalmia and another fetus from a different litter with hind limb abnormalities (brachydactyly and syndactyly). No fetal external malformations or variations were observed in any other group. Similar findings were either observed in a control fetus (microphthalmia), or in the historical control dataset for the laboratory, therefore the findings were not considered drug-related.

A visceral malformation of situs inversus of the abdomen and thoracic cavity was observed in one fetus at 50/2 mg/kg/day and a malformation of retroesophageal aortic arch was observed in one fetus at 200/0 mg/kg/day (RDC-0313 alone). A visceral variation of a smaller than normal thyroid was observed in one fetus at 10/0.5 mg/kg/day, one fetus at 200/6 mg/kg/day, and in two fetuses at 200/0 mg/kg/day (RDC-0313 alone). The visceral malformations/variations were not considered drug-related due to low incidence, the effects were not dose-related, and the findings were reported in the historical control dataset for the laboratory.

Skeletal malformations and variations were observed in RDC-0313 treated groups and were considered drug-related. Bent scapula (a malformation) was observed in one fetus at 200/6 mg/kg/day and in four fetuses from three separate litters at 200/0 mg/kg/day (4.2% and 12% litter incidence, respectively). Bent scapula has not been observed in control fetuses from the historical control dataset and is therefore a drug-related (RDC-0313) finding. Bent ribs (a variation) was observed in five fetuses from two litters at 50/2 mg/kg/day, one fetus at 200/6 mg/kg/day, and in 17 fetuses from 10 litters at 200/0 mg/kg/day (which was statistically significantly increased compared to controls), with a litter incidence of 8%, 4.2%, and 40%, respectively. The litter incidence of bent ribs in historical control dataset is 28%, therefore the findings at 200/0 mg/kg/day are considered drug-related. The incidence of bent scapula and bent ribs was not increased when RDC-0313 was administered in combination with olanzapine.

There was also a drug-related increase in fetuses with sternebra(e) not ossified (a variation) observed at 200/6 mg/kg/day, and at 200/0 mg/kg/day (litter incidence of 87.5% and 88%, respectively compared to a vehicle control litter incidence of 56%). These values were outside the range of the historical control data. The RDC-0313-

related fetal skeletal findings of bent scapula, bent ribs, and non-ossified sternebrae were also observed in the rat embryofetal development study with RDC-0313 alone (study 825-0282) and are therefore related to RDC-0313 treatment.

Dose RDC-0313/Olanzapine (mg/kg/day)	0/0	10/0.5	50/2	200/6	200/0
<b>Fetal Observations</b>					
<b>External Malformations and Variations</b>	-	-	-	-	-
<b>Visceral Malformations and Variations</b>	-	-	-	-	-
<b>Skeletal Malformations</b>					
No. Litters/Fetuses Evaluated	25/164	25/161	25/151	24/135	25/160
Scapula, Bent					
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	3 (12.0)
No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	4 (2.5)
<b>Skeletal Variations</b>					
No. Litters/Fetuses Evaluated	25/164	25/161	25/151	24/135	25/160
Rib(s), Bent					
No. Litters (%)	0 (0.0)	0 (0.0)	2 (8.0)	1 (4.2)^	10 (40.0)**
No. Fetuses (%)	0 (0.0)	0 (0.0)	5 (3.3)	1 (0.7)	17 (10.6)
Sternebra(e), Not ossified					
No. Litters (%)	14 (56.0)	13 (52.0)	13 (52.0)	21 (87.5)	22 (88.0)
No. Fetuses (%)	26 (15.9)	25 (15.5)	22 (14.6)	63 (46.7)	59 (36.9)

Abbreviations: - = No noteworthy findings; GD = Gestation Day; NA = Not applicable; No. = Number; TK = Toxicokinetic; \* = Significantly different from control; (p<0.05); \*\* = Significantly different from control; (p<0.01); ^ = Significantly different from Group 5; (p<0.05); ^^ = Significantly different from Group 5; (p<0.01)

[Source: NDA 213378, Toxicology tabulated summary]

### 9.3 Prenatal and Postnatal Development

**Study title:** An Oral (Gavage) Study of the Effects of RDC-0313 on Pre- and Postnatal Development, Including Maternal Function in Rats

Study no.: AT-0313-38

Study report location: SDN 1

Conducting laboratory and location:

(b) (4)

Date of study initiation: 1/27/15

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RDC-0313-02, lot # E555FP-14-001, 99.8%

#### Key Study Findings

- No drug-related adverse effects on any maternal F<sub>0</sub> parameters. NOAEL for maternal toxicity is 100 mg/kg/day.
- 100 mg/kg/day: decrease in F<sub>1</sub> pup survival from birth to PND 4, decreased F<sub>1</sub> pup birth weights and body weight gain during the pre-weaning and post-weaning phases.
- No drug-related effects on F<sub>1</sub> sexual maturation, reproduction, neurobehavioral function, and no effects on F<sub>2</sub> embryo survival.
- NOAEL for F<sub>1</sub> survival and growth is 30 mg/kg/day, which is approximately 36 times the MRHD of 10 mg SAM based on AUC.
- NOAEL for F<sub>1</sub> reproductive and F<sub>2</sub> embryonic toxicity is 100 mg/kg/day, which is approximately 188 times the MRHD of 10 mg SAM based on AUC.

#### Methods

Doses: **0, 10, 30, 100 mg/kg/day**

Frequency of dosing: Once daily to F<sub>0</sub> females from Gestation day (GD) 6 to Lactation day (LD) 20

Dose volume: 10 ml/kg

Route of administration: Oral gavage

Formulation/Vehicle: Solution/Sterile water for injection

Species/Strain: Bred female rat/Sprague Dawley from (b) (4)

~14 weeks old at dosing initiation

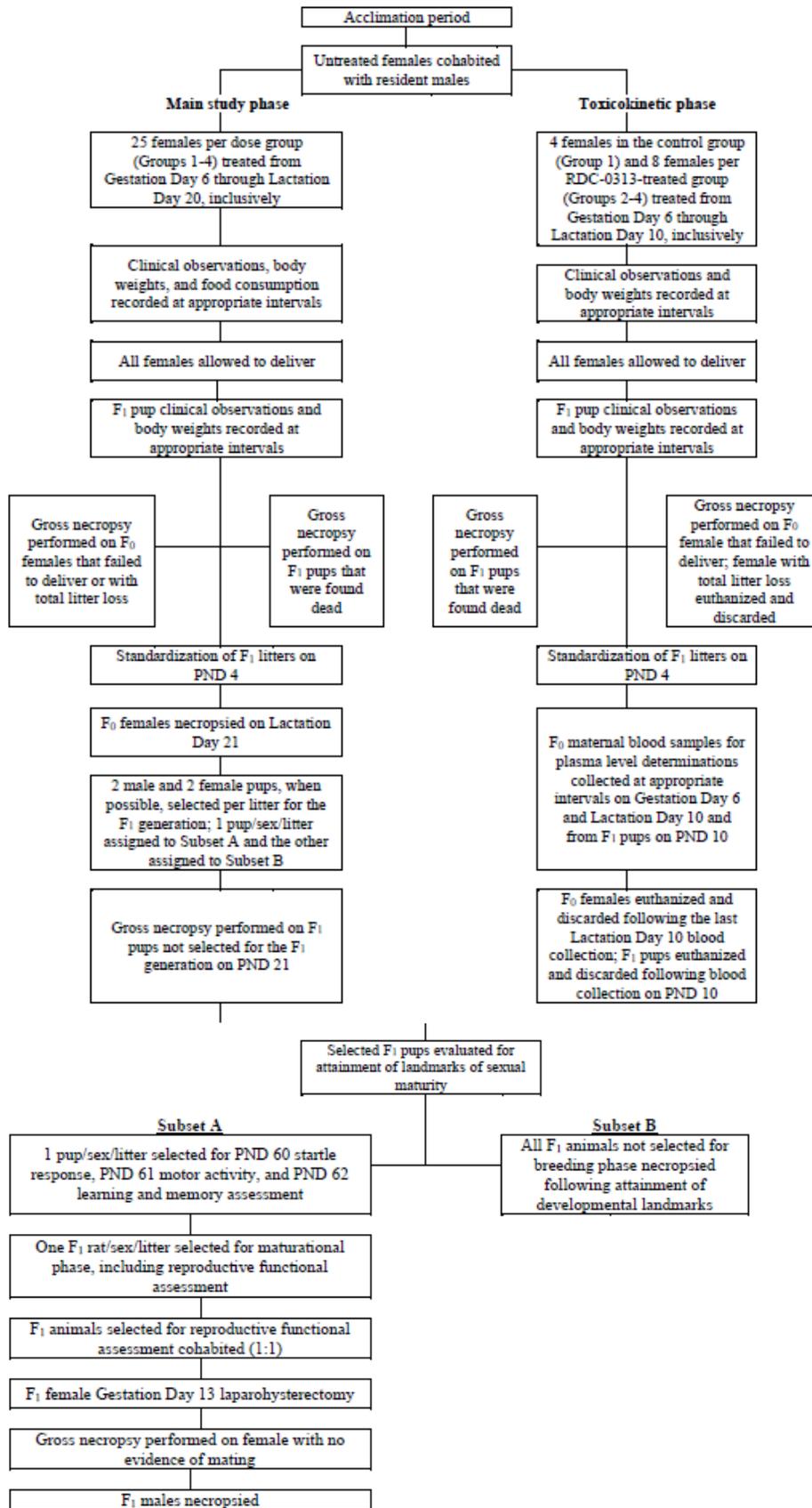
Number/Sex/Group: 25/group

Satellite groups: Toxicokinetics: 4/control group, 8/drug-treated groups administered vehicle or drug once daily from GD 6 to LD 10

Study design: See Applicant's diagram below

Deviation from study protocol: Deviations noted, but none affected study integrity.

#### Study Design:



## Observations and Results:

F<sub>0</sub> Dams

Survival:

Clinical signs:

Body weight:

Food consumption:

Uterine content:

Necropsy observation:

Toxicokinetics:

All F<sub>0</sub> females survived to scheduled necropsy. Salivation and/or clear material around the mouth was observed at 100 mg/kg/day approximately 1 hour after dosing throughout the treatment period.

Body weight gain was statistically significantly lower than controls during the overall gestation period (GD 6-20) for all drug-treated groups. Mean absolute body weight values for all drug-treated groups were lower than controls ( $\leq 4.7\%$  compared to controls) from GD 9-20, but did not reach statistical significance. The effects on body weight were small in magnitude and not considered adverse. The lower body weights corresponded with lower food consumption. There were no drug-related effects on body weight during the lactation period.

Food consumption was statistically significantly decreased in all drug-treated groups compared to controls during the gestation period. The effects were drug-related, but small and therefore not considered adverse. The finding corresponded with lower body weights in the drug-treated groups.

There were no drug-related effects on the number of implantation sites, number of pups born, sex at birth, or litter size.

There were no drug-related macroscopic findings in F<sub>0</sub> females.

F<sub>0</sub>: Exposure (AUC and C<sub>max</sub>) to parent drug in F<sub>0</sub> rats was greater than dose-proportional, except for C<sub>max</sub> values between 30 and 100 mg/kg/day. Exposure (AUC) to metabolite, RDC-9986, increased almost dose-proportionally. The metabolite to parent ratio was highest in the low dose group (0.47) and decreased with increasing dose (0.27 and 0.14 at 30 and 100 mg/kg/day, respectively).

TK in F<sub>1</sub> pups: Plasma exposure to parent and metabolite RDC-9986 was detected in male and female F<sub>1</sub> pups at both time points of 2 and 6 hours post-dose of F<sub>0</sub> dams on PND 10 (LD 10). Exposure in rat pups to parent and metabolite was <11% and <13% of concentrations in maternal rats. Exposures to parent and metabolite increased almost dose-

proportional from 10 to 30 mg/kg/day and greater than proportional from 30 to 100 mg/kg/day.

Dosing Solution Analysis All dosing formulations were homogenous, and concentrations were within the acceptable range (85% to 115% of target of concentration).

Other: There were no drug-related effects on gestation length or parturition. One high dose female had a total litter loss.

**Text Table 3. Toxicokinetic Parameters for RDC-0313 and RDC-9986 in Female Rats following Oral Administration of RDC-0313**

Analyte	Interval	TK Parameters	10 mg/kg/day RDC-0313	30 mg/kg/day RDC-0313	100 mg/kg/day RDC-0313
RDC-0313	GD 6	AUC <sub>last</sub> (ng*h/mL)	3010	12,600	71,600
		C <sub>max</sub> (ng/mL)	773	4050	8170
		T <sub>max</sub> (h)	2	1	1
RDC-0313	LD 10	AUC <sub>last</sub> (ng*h/mL)	2680	13,200	68,500
		C <sub>max</sub> (ng/mL)	814	4720	7080
		T <sub>max</sub> (h)	1	1	2
RDC-9986	GD 6	AUC <sub>last</sub> (ng*h/mL)	1350	3150	10,900
		C <sub>max</sub> (ng/mL)	277	593	843
		T <sub>max</sub> (h)	2	1	1
		Metabolite/Parent Ratio	0.45	0.25	0.15
RDC-9986	LD 10	AUC <sub>last</sub> (ng*h/mL)	1250	3600	9340
		C <sub>max</sub> (ng/mL)	309	841	925
		T <sub>max</sub> (h)	1	1	1
		Metabolite/Parent Ratio	0.47	0.27	0.14

GD = Gestation Day    LD = Lactation Day

**Text Table 4. Mean Concentrations of RDC-0313 and RDC-9986 in Plasma of Male and Female Rat Pups on Postnatal Day 10 following Oral Administration of RDC-0313 at 10, 30, or 100 mg/kg/day to Pregnant Rats**

Analyte	Time Interval (h)	10 mg/kg/day RDC-0313 Mean (ng/mL)	30 mg/kg/day RDC-0313 Mean (ng/mL)	100 mg/kg/day RDC-0313 Mean (ng/mL)
<u>Males</u>				
RDC-0313	2	4.46	19.9	171
	6	7.45	36.1	152
RDC-9986	2	2.18	8.45	64.9
	6	6.23	18.8	80.0
<u>Females</u>				
RDC-0313	2	5.63	21.5	200
	6	8.19	36.6	212
RDC-9986	2	2.47	8.60	64.1
	6	5.95	18.5	96.9

N=4

#### F<sub>1</sub> Generation

##### Survival:

There was a statistically significant decrease in initial pup survival from postnatal day (PND) 0 to PND 1 from pups of 100 mg/kg/day treated females, 92.1% compare to 99.0% for controls. There was a greater decrease in pup survival from birth to PND 4 in pups from high dose treated dams, 83.2% compared to 97.2% for controls.

##### Clinical signs:

There was an increased incidence of pups with cool and/or pale bodies from 100 mg/kg/day F<sub>0</sub> animals compared to control treated dams.

##### Body weight:

Mean absolute body weights for male and female F<sub>1</sub> pups from 100 mg/kg/day treated dams were statistically significantly decreased compared to controls during the entire pre-weaning period (PND 1 to PND 21), with a maximum decrease of 18% compared to controls for both male and female pups. Mean body weights for male and female pups from 30 mg/kg/day treated dams were also statistically significantly decreased compared to controls on PND 21 (8% compared to controls). Body weight change for male and female pups from 100 mg/kg/day treated dams were statistically significantly decreased compared to controls during PND 1 to 10, and PND 17 to 21. Body weight change for male and female pups from 30 mg/kg/day treated dams was

	also statistically significantly decreased compared to controls from PND 17 to 21. The statistically significant decrease in body weight for male and female pups from 100 mg/kg/day treated dams compared to controls continued into the post-weaning phase, PND 21 to 70 and PND 84.
Food consumption:	A few pups that were found dead from the 100 mg/kg/day group had little or no milk in their stomachs.
Physical development:	The mean age of balanopreputial separation for F <sub>1</sub> males and vaginal patency for F <sub>1</sub> females was unaffected by maternal drug-treatment.
Neurological assessment:	There was no significant drug-related effect on the auditory startle response, motor activity, or learning memory (swimming ability in Biel maze) assessed on selected pups on PND 60, 61, or 62, respectively.
Reproduction:	There were no drug-related effects on reproductive performance of F <sub>1</sub> males or females.
Other:	There were no macroscopic findings upon necropsy that were attributed to maternal drug exposure.

F<sub>2</sub> Generation: Mated F<sub>1</sub> females were not allowed to give birth but were necropsied on gestation day 13 and uterine contents were examined. Uterine parameters evaluated included pre-implantation loss, post-implantation loss and the mean numbers of viable embryos, corpora lutea, and implantation sites. There was a statistically significant increase in pre-implantation loss in the mated F<sub>1</sub> females from the 100 mg/kg/day group compared to controls. However, the difference was due to a low mean value in the control group that was outside the historical control range and therefore the finding is most likely not drug-related. There were no drug-related effects on any other uterine parameters.

## 9.4 Juvenile Animal Studies

A juvenile animal toxicity study entitled “An Oral (Gavage) Juvenile Toxicity Study of RDC-0313 and Olanzapine in Sprague Dawley Rats, with a 6-Week Recovery and a Toxicokinetic Phase” (study no. AT-0313-47) is currently on-going. The study is being conducted under the corresponding IND (IND 114375).

# 10 Special Toxicology Studies

## 10.1 Phototoxicity assessment

The ultraviolet (UV) and visible absorbance of 10 µM SAM was measured in methanol over a range of 290 nm to 700 nm (Report 702-02575). One absorption peak was observed in the UVB range at 309 nm that had a molar extinction coefficient value > 1000 L mol<sup>-1</sup>cm<sup>-1</sup>. No dedicated in vitro or in vivo phototoxicity studies were conducted with SAM alone or the combination of OLZ and SAM. The Applicant considered the phototoxic potential of systemically administered SAM to humans to be very low, and

there were no indicators of phototoxicity in clinical trials with SAM alone or the combination of OLZ and SAM. According to ICH-S10, UVB-induced phototoxicity is rarely a problem for drugs with systemic exposure, because UVB minimally penetrates beyond the epidermis. However, it should be noted that based on tissue distribution studies in rats, SAM binds to melanin-containing tissues, including skin, which could contribute to potential phototoxicity.

## 11 Integrated Summary and Safety Evaluation

Lybalvi is a fixed-dose combination product of samidorphan (SAM), an NME drug, and olanzapine (OLZ), an approved drug product. The NDA relies on the Agency's previous findings of nonclinical safety for OLZ, Zyprexa NDA 020592, approved in 1996 as the listed drug. Pertinent nonclinical data for OLZ will be included in the label for Lybalvi based on the most recently approved Zyprexa label. The maximum recommended human dose (MRHD) for the combination drug product is 20 mg/10 mg (OLZ/SAM). OLZ is an atypical antipsychotic that interacts with a broad set of receptors. SAM is an antagonist at the mu-opioid receptor and a partial agonist at kappa-opioid receptors. The Applicant's rationale for the combination of OLZ and SAM is attenuation of OLZ's weight gain effects by SAM, while maintaining antipsychotic activity of OLZ. The combination of OLZ and SAM represents a novel pharmacological approach to the treatment of schizophrenia and bipolar I disorder. A complete nonclinical safety assessment, including pharmacology, safety pharmacology, abuse liability, toxicology, and pharmacokinetic assessments, has been conducted with SAM alone. Additionally, the NDA contains results of evaluations of the combination of OLZ and SAM to further support the pharmacology, pharmacokinetics, and toxicology of the combination drug product.

In vitro assays conducted by the Applicant demonstrate that SAM binds with high affinity to mu- and kappa-opioid receptors and with lower affinity to delta-opioid receptors,  $K_i$  values of 0.052, 0.23, and 2.7 nM, respectively. SAM acts as an antagonist at mu-opioid receptors ( $IC_{50}$  of 0.88 nM) and as a partial agonist at both kappa-, and delta-opioid receptors with  $EC_{50}$  values of 3.2 and 1.8 nM, respectively. SAM blocked the antinociceptive effects of morphine in rats and reversed some of the fentanyl-induced respiratory depression effects in dogs and monkeys, demonstrating that SAM has opioid antagonistic activity in vivo. Based on the approved label for Zyprexa, OLZ acts as a high affinity antagonist at serotonin 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>6</sub>, dopamine D<sub>1</sub>-D<sub>4</sub>, histamine H<sub>1</sub>, and adrenergic  $\alpha_1$  receptors; and binds with moderate affinity to 5-HT<sub>3</sub> and muscarinic M<sub>1</sub>-M<sub>5</sub> receptors. In vivo pharmacodynamic studies were conducted in rodents and non-human primates with the combination of OLZ and SAM. SAM attenuated OLZ-induced increase in extracellular levels of dopamine and its metabolites in the rat nucleus accumbens in response to a high fat diet. Co-administration of SAM did not affect the ability of OLZ to inhibit amphetamine-induced hyperlocomotor activity in female rats (a common rodent behavioral model used to measure antipsychotic-like activity of drugs) indicating that SAM does not interfere with the antipsychotic efficacy of OLZ. Co-administration of SAM attenuated OLZ-induced weight gain and adipose accumulation in rats and non-human primates. SAM attenuated OLZ-induced decreases in glucose utilization when in female rats; but did not prevent OLZ-induced liver insulin

resistance or have any effects on HbA1c levels or glucose tolerance in non-human primates.

There are two major human circulating metabolites of SAM, RDC-9986 (N-dealkylated metabolite) and RDC-1066 (N-oxide of SAM). RDC-9986 binds with high affinity to mu-opioid receptors ( $K_i$  of 0.26 nM) and much lower affinity to kappa- and delta-opioid receptors,  $K_i$  values of 23 and 56 nM, respectively. RDC-9986 functions as an agonist at those receptors in vitro, with  $EC_{50}$  values of 17, 53, and 130 nM, respectively. In vivo rodent behavioral assays with RDC-9986 suggest that it has some partial opioid agonist properties. Metabolite RDC-1066 binds with significantly lower affinity to mu-, kappa-, and delta-opioid receptors ( $K_i$  values of 8.1, 110, and 280 nM, respectively) compared to both SAM and RDC-9986, and therefore it's overall contribution to the pharmacodynamic of SAM at clinically relevant drug concentrations is most likely minimal. Neither SAM or metabolites RDC-9986 and RDC-1066 significantly inhibited binding to off-target receptors in vitro. The half-lives of both metabolites are longer than that of SAM. The overall pharmacodynamic effect of these major metabolites in combination with SAM at clinically relevant concentrations, at steady state and after drug cessation, is unknown.

In safety pharmacology studies, SAM and metabolite RDC-9986 were not significant hERG channel blockers ( $IC_{50}$  values of 28.19 and >280  $\mu$ M, respectively). SAM did not have any significant adverse effects on cardiovascular or respiratory parameters in dogs at doses up to 10 mg/kg. SAM had effects on CNS and neurobehavioral activity in rats including reduced response during hand-to-hand transfer, increased salivation, reduced crossing and rearing in an open-field test, reduced rectal temperature compared to control, stereotypical behaviors such as rubbing of chins on cage surfaces and excessive burrowing, however all of these effects were only observed at the highest dose of 350 mg/kg. The no effect level (NOEL) dose of 35 mg/kg, is approximately 15 times the MRHD based on  $C_{max}$  and approximately 3 times based on AUC. The Applicant noted that similar behaviors have been described with other drugs that modulate opioid receptors.

The pharmacokinetic profile of SAM was different in rats, compared to dogs and humans. Oral bioavailability was low in rats (15%), and higher in dogs (39%-66%) which was closer to that of humans. There is a significant sex difference in exposure and metabolism of SAM in rats with females having much higher exposure to parent drug than males, and males having higher exposure to metabolites than females. There was no significant sex difference in exposure to parent drug or metabolites in dogs and humans. SAM is highly distributed to tissues in rats and was found to bind to melanin-containing tissues including skin and eyes and is mainly excreted in urine in rats and dogs. Co-administration of OLZ with SAM did not have any significant effects on exposure or TK parameters of SAM or RDC-9986, including  $T_{max}$  and  $T_{1/2}$ , in dogs and pregnant rats, compared to SAM administration alone. Similarly, SAM did not have any significant effects on exposure of OLZ when co-administered compared to administration of OLZ alone in dogs and pregnant rats.

Toxicity of SAM was evaluated in Sprague-Dawley rats and Beagle dogs up to 6 months and 9 months in duration, respectively. Common drug-related effects in both species included decrease in body weight which correlated with decreases in food intake. In rats, a single dose administration study and a 2-week repeat-dose study were conducted using oral doses of 35, 110, or 350 mg/kg, with 350 mg/kg/day being the maximum feasible dose based on solubility. Toxicities observed after 2-weeks of dosing included a significant decrease in body weight and food consumption, and histopathological findings in the lungs, liver, and heart. A 13-week repeat-dose rat study with a 4-week recovery period was conducted using doses of 25, 75, and 250 mg/kg/day. In this study, there was a dose-related decrease in body weight in males, up to 20% compared to controls, with a corresponding decrease in food consumption. Histopathological findings were observed in the kidney (nephropathy), heart (cardiomyopathy), and liver (hepatocellular hypertrophy) of male and female rats at 75 and/or 250 mg/kg/day. The effects were all fully reversible except for the liver findings in males, where there was some evidence of partial reversibility. Changes in the pancreas (Islet cell vacuolation) and teeth (dentin dysplasia and pulp cavity metaplasia) were only observed in high dose males at exposures greater than 200 times the MRHD based on AUC. The NOAEL in the 13-week rat study was 25 mg/kg/day, which is approximately 5 times and 51 times the MRHD based on AUC for male and female rats, respectively. Doses of 0.5, 5, and 50 mg/kg/day were used in the pivotal 6-month chronic toxicity study with a 4-week recovery period. The main toxicity observed was a significant decrease in body weight in high dose males and females, 24% and 9% compared to controls, respectively, which correlated with a decrease in food consumption. The effects on body weight were partially reversible. The only histopathological finding was liver hepatocellular cytoplasmic vacuolation in high dose males, which was partially reversible. There were no histopathological findings in females, even though females had higher exposure to the parent drug, suggesting that the effects observed in male rats may be due to higher exposure to the RDC-9986 metabolite. The NOAEL was 5 mg/kg/day, which is approximately 0.4 and 5 times the MRHD based on AUC for males and females, respectively.

A single-dose oral toxicity study was conducted in Beagle dogs using doses of 3, 10, 20, and 40 mg/kg. Toxicities included clinical signs of excessive salivation, hypoactivity, and tremors at doses  $\geq 10$  mg/kg and pupil dilation in the high dose of 40 mg/kg. A 2-week repeat-dose oral gavage study with a 2-week recovery period evaluated initial doses of 2, 6, and 20 mg/kg/day, however dosing was stopped after a few days due to excessive salivation, possible regurgitation, and struggling with dosing. The study was restarted after a dosing holiday using lower doses of 1, 3, and 10 mg/kg/day. Findings included adverse emesis and excessive salivation at 10 mg/kg/day, slight decreases in body weight and food consumption. The NOAEL was considered to be 3 mg/kg/day. Both the 13-week and 9-month repeat-dose studies with 4-week recovery periods also evaluated doses of 1, 3, and 10 mg/kg/day. Similar to the 2-week study, clinical signs of excessive salivation, lip smacking, and head shaking occurred at doses  $\geq 3$  mg/kg/day in both the 13-week and 9-month studies. A decrease in body weight gain was observed in the 13-week study in high dose males and in females at all doses with partial recovery. The NOAEL was 3 mg/kg/day in the 13-week study. The effect on body

weight was more pronounced and considered adverse with longer drug treatment in the 9-month study as shown by a dose-related and statistically significant decrease in mean body weight in males and females at 3 and 10 mg/kg/day (>10% compared to controls), which was partially reversible. Exposure to parent increased greater than dose-proportional and there was modest accumulation after repeated dosing. Exposure to metabolite RDC-9986 increased roughly dose-proportional. The NOAEL was 1 mg/kg/day for males and females in the 9-month study, which is approximately equal to exposure levels in humans at the MRHD based on AUC.

A toxicological evaluation of the combination of OLZ and SAM was investigated in a 13-week repeat-dose oral toxicity study in dogs that were co-administered OLZ and SAM at doses of 0/0, 5/0, 0/10, 1.5/3, and 5/10 mg/kg/day OLZ/SAM. No new toxicities were identified when OLZ and SAM were co-administered compared to toxicities identified with OLZ and SAM alone. CNS-related clinical signs including tremors and ataxia, and gastrointestinal-related signs including emesis and feces changes were observed in males and females after treatment with OLZ, SAM, and the combination. Reversible organ weight changes with accompanying microscopic findings were observed in male and female reproductive tract organs (epididymides, prostate, and mammary gland) and were attributed to OLZ. Non-adverse, partially reversible decreases in thymus weights with corresponding microscopic findings of lymphoid depletion were observed in males only after treatment with OLZ, SAM, and the combination. The NOAEL is 5/10 mg/kg/day OLZ/SAM. The NOAEL for SAM was 10 mg/kg/day with or without 5 mg/kg/day OLZ.

SAM was tested in a standard battery of GLP genetic toxicology studies including an in vitro Ames assay, in vitro mammalian chromosomal aberration assay using human peripheral blood lymphocytes, and in vivo mouse micronucleus test using male ICR mice administered single oral doses up to 420 mg/kg. All studies were adequately conducted, and the results were negative. Carcinogenicity of SAM was evaluated in a 6-month transgenic mouse and a 2-year rat study; SAM was not carcinogenic in either species. Tg.rash2 mice were administered SAM by oral gavage at doses of 125, 250, and 500 mg/kg/day for 26 consecutive weeks. There was a statistically significant increase in mortality for low and mid dose males, and high dose females compared to respective vehicle controls. The cause of death was undetermined for most males and for all females; however, it was most likely different for males and females due to different dose-response and temporal relationships. The Applicant hypothesized the deaths may be related to opioid-agonist toxicities from higher exposure to the RDC-9986 metabolite, which is a mu-opioid partial agonist, compared to parent drug in the low and mid dose male groups compared to high dose males and females. The study was negative, as there were no statistically significant drug-related neoplastic findings in either males or females. Sprague Dawley rats were administered SAM by oral gavage at doses of 20, 35, and 75 mg/kg/day for males and 15, 30, and 60 mg/kg/day for females for 95 consecutive weeks. All male and female groups were prematurely terminated due to low survival numbers in the respective control groups. There was a statistically significant decrease in survival rate for high dose females compared to controls. The study was negative, as there were no statistically significant drug-related

neoplastic findings in either males or females. Safety margins at 75 mg/kg/day for males and 60 mg/kg/day for females are approximately 32 and 237 times, respectively compared to exposure at the MRHD of 10 mg SAM based on AUC.

Developmental and reproductive toxicity studies were conducted with SAM in rats and rabbits and an embryofetal development study was conducted with the combination of OLZ/SAM in rats. Oral administration of SAM at doses of 10, 30, and 100 mg/kg/day to male rats starting 28 days prior to pairing males with untreated females and continuing throughout mating and the post-mating period did not result in any drug-related effects on male fertility parameters or any adverse effects on early embryonic development of fetuses. SAM administration at doses of 30, 150, and 450 mg/kg/day to female rats starting 14 days prior to pairing with untreated males and continuing throughout mating and post-mating period until gestation day 7 did not result in any drug-related effects on reproductive or fertility parameters, including mating and pregnancy outcome. Uterine and ovary weights were increased at 150 and 450 mg/kg/day, estrous cycle lengths were increased at 450 mg/kg/day, and the total number of estrous cycles were increased at all dose levels. In an embryofetal development study conducted in pregnant rats administered oral doses of SAM at 25, 100, and 300 mg/kg/day during organogenesis (gestation days 6 to 17), maternal toxicity of decreased food consumption and decreased body weight occurred at all doses. There was an increase in the number of resorptions and decreased litter size at 300 mg/kg/day. Drug-related effects of decreased fetal weights and increased skeletal variations (bent ribs, non-ossified sternbrae, decrease in rudimentary ribs) occurred at 100 and 300 mg/kg/day. There was a slight, but statistical increase in the total number of malformations at 300 mg/kg/day compared to controls. Pregnant rabbits treated with SAM during organogenesis (gestation days 7 to 19) at oral doses of 10, 30, and 90 mg/kg/day resulted in no drug-related effects on any uterine parameters, or adverse effects on fetuses, but adverse maternal toxicity of decreased body weight gain and food consumption was observed at all doses. An embryofetal development study was also conducted in pregnant rats using the combination of SAM/OLZ at doses of 0/0, 10/0.5, 50/2, 200/6, and 200/0 mg/kg/day. Maternal toxicity was observed at all dose levels which included decreased body weight and food consumption; a maternal NOAEL was not determined. Reduced mean fetal body weights were observed at 200/6 and 200/0 mg/kg/day and increased resorptions and post-implantation loss, with correlating lower mean viable fetuses and litter size, were observed with the high dose combination of 200/6 mg/kg/day. An increase in bent scapula, bent ribs, and fetuses with sternbra(e) not ossified was observed at 200/6 mg/kg/day and 200/0 mg/kg/day, which is approximately 6 and 448 times the MRHD of 20/10 mg OLZ/SAM based on AUC, respectively for OLZ and SAM. The embryofetal NOAEL is 50/2 mg/kg/day SAM/OLZ, which is approximately 80 and 0.9 times the MRHD of 20/10 mg OLZ/SAM based on AUC, respectively. In a pre- and postnatal development study, pregnant rats were administered SAM at oral doses of 10, 30, and 100 mg/kg/day from gestation day 6 through lactation day 20. There was no evidence of any maternal toxicity or effects on pup sexual maturation, reproduction, neurobehavioral function, and there were no effects on F2 embryo survival. There was a drug-related decrease in pup birth weights and pup body weight gain at 100 mg/kg/day.

The Applicant conducted an adequate assessment of potentially genotoxic impurities according to ICH M7(R1). The specification limit of NMT <sup>(b) (4)</sup> % for the non-genotoxic impurity <sup>(b) (4)</sup> is acceptable from a nonclinical standpoint based on qualification in nonclinical toxicity studies. Exposure to the major human metabolites, RDC-9986 and RDC-1066, in animals used in the chronic toxicity studies, embryofetal development studies, and the rat 2-year carcinogenicity study are higher than exposures in humans at the MRHD of 10 mg SAM. Therefore, these two major human metabolites have been adequately qualified in nonclinical studies.

Overall, an adequate nonclinical assessment of SAM and the combination of OLZ and SAM was conducted to support the NDA for the treatment of schizophrenia and bipolar I disorder at a maximum recommended human dose of 20 mg/ 10 mg OLZ/SAM. The NDA is approvable from a nonclinical standpoint.

**Table 9: Safety margins from safety pharmacology and toxicity studies compared to exposures of samidorphan at the MRHD in humans.**

System	Study/ Species	Dose (mg/kg/day)	Findings	C <sub>max</sub> (ng/mL) in M/F	AUC (ng*hr/mL) in M/F <sup>a</sup>	Nonclinical to Clinical C <sub>max</sub> Multiple (x) in M/F <sup>b</sup>	Nonclinical to Clinical AUC Multiple (x) in M/F <sup>b</sup>
Cardio-vascular	Dog Cardio-vascular/ Respiratory Study (AT-0313-10)	10	↑ QT <sub>c</sub> ↓ Systolic BP ↓ Mean arterial BP ↑ Heart rate ↓ Contractility parameters (all non-adverse)	1690/1980 <sup>c</sup>	5580/9060 <sup>c</sup>	37/43	15/25
		3	No substantive findings	525/439 <sup>d</sup>	1480/1430 <sup>d</sup>	11/9.5	4.1/3.9
Respiratory	Dog Cardio-vascular/ Respiratory Study (AT-0313-10)	10	No treatment-related findings	1690/1980 <sup>c</sup>	5580/9060 <sup>c</sup>	37/43	15/25
CNS	Rat CNS/ Neuro-behavioral Study (AT-0313-11)	350	↓ Rectal temperature ↓ open field spontaneous activity ↓ rearing ↓ resistance to hand-to-hand transfer Hypersalivation and stereotypic behavior	12,400 <sup>e</sup> /NA	63,700 <sup>e</sup> /NA	270/NA	175/NA
		35	NOEL	1080 <sup>f</sup> /NA	2180 <sup>f</sup> /NA	24/NA	6.0/NA

Abbreviations: BP=blood pressure; CNS=central nervous system; F=female; M=male; NA=not available; NOEL=no-observed-effect level; QT<sub>c</sub>=corrected QT interval via regression method; SAM=samidorphan (RDC-0313); ↓=decreased; ↑=increased

<sup>a</sup> AUC<sub>∞</sub> or AUC<sub>0-24h</sub> values following a single oral SAM administration are reported from toxicokinetic bridging studies in rats (AT-0313-41) and dogs (AT-0313-43).

<sup>b</sup> Exposure multiples were calculated relative to steady-state exposure data in humans at 10 mg samidorphan (MRHD) following repeated daily oral administration of ALKS 3831 20/10 from Study ALK3831-A104; C<sub>max</sub> and AUC<sub>0-24h</sub> of 46.0 ng/mL and 364 ng\*hr/mL for SAM, 15.1 ng/mL and 186 ng\*hr/mL for RDC-9986, and 9.0 ng/mL and 61.1 ng\*hr/mL for RDC-1066. Exposure multiples were calculated relative to total SAM exposure as plasma protein binding was similar in humans and nonclinical species.

<sup>c</sup> Day 1 exposure data at 10 mg/kg SAM from Study AT-0313-43

<sup>d</sup> Day 1 exposure data at 3 mg/kg SAM from Study AT-0313-43

<sup>e</sup> Day 1 exposure data at 350 mg/kg SAM from Study AT-0313-41

<sup>f</sup> Exposure values in males at 35 mg/kg SAM were estimated assuming linear increases in exposure from 25 to 50 mg/kg from Study AT-0313-41 (Day 1 exposure data)

[Source: NDA 213378, Nonclinical overview]

Target	Study/Species	Findings	Dose (mg/kg/day)	C <sub>max</sub> (ng/mL) in M/F	AUC (ng*hr/mL) in M/F <sup>a</sup>	Nonclinical to Clinical C <sub>max</sub> Multiple (×) in M/F <sup>b</sup>	Nonclinical to Clinical AUC Multiple (×) in M/F <sup>b</sup>
CNS	4-Week Carcinogenicity Dose Range-finding in Mice (AT-0313-27)	Tremors, ataxia	600	31,833/42,800	192,783/429,017	692/930	530/1179
		No adverse effects	300 <sup>c</sup>	22,000/29,000	50,296/124,674	478/630	138/343
	Rat Embryofetal Development Range-finding (AT-0313-20)	Tremors and convulsions in F	1000	NA/66,300 <sup>d</sup>	NA/760,000 <sup>d</sup>	NA/1442	NA/2090
		No adverse effects	450	NA/34,500	NA/296,000	NA/750	NA/813
	39-Week Repeat Dose in Dogs with 4-Week Recovery (AT-0313-19)	Seizures (4 occurrences) in 1 F dog (considered incidental)	10	NA/2200	NA/10,700	NA/48	NA/29
		No effects	3	NA/557	NA/2570	NA/12	NA/7.1
5-Day Repeat Dose in Dogs (AT-0313-02)	Tremors and lordosis	20	3470/2820	19,000/16,300	75/61	52/45	
	No adverse effects	10	2460/2200 <sup>e</sup>	13,800/10,700 <sup>e</sup>	390/349	251/195	
Liver	26-Week Repeat Dose in Rats with 4-Week Recovery (AT-0313-16)	Hepatocellular vacuolation in M	50	1650/NA	4890/NA	36/NA	13/NA
		No adverse effects	5	75.5/NA	159/NA	1.6/NA	0.44/NA
	13-Week Repeat Dose in Rats with 4-Week Recovery (AT-0313-18)	Hepatocellular vacuolation in F	250	NA/33,800	NA/342,000	NA/735	NA/940
		No adverse effects	75	NA/24,400	NA/102,000	NA/530	NA/280

Target	Study/Species	Findings	Dose (mg/kg/day)	C <sub>max</sub> (ng/mL) in M/F	AUC (ng*hr/mL) in M/F <sup>a</sup>	Nonclinical to Clinical C <sub>max</sub> Multiple (×) in M/F <sup>b</sup>	Nonclinical to Clinical AUC Multiple (×) in M/F <sup>b</sup>
Kidney	13-Week Repeat Dose in Rats with 4-Week Recovery (AT-0313-18)	Nephropathy	250	13,500/33,800	75,600/342,000	293/735	208/940
		No adverse effects	75	3330/24,400	9730/102,000	72/530	27/280
Heart	13-Week Repeat Dose in Rats with 4-Week Recovery (AT-0313-18)	Cardiomyopathy	250	13,500/33,800	75,600/342,000	293/735	208/940
		No adverse effects	75	3330/24,400	9730/102,000	72/530	27/280
Pancreas	13-Week Repeat Dose in Rats with 4-Week Recovery (AT-0313-18)	Cytoplasmic vacuolation of islet cells in M	250	13,500/NA	75,600/NA	293/NA	208/NA
		No adverse effects	75	3330/NA	9730/NA	72/NA	27/NA
Teeth	13-Week Repeat Dose in Rats with 4-Week Recovery (AT-0313-18)	Dentin dysplasia and pulp cell metaplasia in M	250	13,500/NA	75,600/NA	293/NA	208/NA
		No adverse effects	75	3330/NA	9730/NA	72/NA	27/NA
Developmental	Rat Embryofetal Development (AT-0313-22)	Skeletal malformations in fetuses	100	NA/7300	NA/90,100	NA/159	NA/248
		No adverse effects	25	NA/2100	NA/10,500	NA/46	NA/29

Target	Study/Species	Findings	Dose (mg/kg/day)	C <sub>max</sub> (ng/mL) in M/F	AUC (ng*hr/mL) in M/F <sup>a</sup>	Nonclinical to Clinical C <sub>max</sub> Multiple (×) in M/F <sup>b</sup>	Nonclinical to Clinical AUC Multiple (×) in M/F <sup>b</sup>
Developmental (continued)	Rat Pre- and Postnatal Development (AT-0313-38)	↓ Pup survival at birth to PND 4; ↓ pup birth weights and weight gains from birth to PND 10, with ↓ weight gains continuing to PND 84	100	NA/7080	NA/68,500	NA/154	NA/188
		No adverse effects	30	NA/4720	NA/13,200	NA/103	NA/36

Abbreviations: CNS=central nervous system; F=female; M=male; NA=not applicable; NOAEL=No-observed-adverse-effect level; PND=postnatal day; SAM=samidorpham; ↓=decreased

<sup>a</sup> AUC<sub>last</sub> or AUC<sub>0-24h</sub> values at steady state are reported from toxicology or toxicokinetic bridging studies. At 600 mg/kg/day in Study AT-0313-27, the Day 1 AUC value is reported due to early termination of the dose group.

<sup>b</sup> Exposure multiples were calculated relative to steady-state exposure data in humans at 10 mg samidorphan (MRHD) following repeated daily oral administration of ALKS 3831 20/10 from Study ALK3831-A104; C<sub>max</sub> and AUC<sub>0-24h</sub> of 46.0 ng/mL and 364 ng\*hr/mL for SAM, 15.1 ng/mL and 186 ng\*hr/mL for RDC-9986, and 9.0 ng/mL and 61.1 ng\*hr/mL for RDC-1066. Exposure multiples were calculated relative to total SAM exposure as plasma protein binding was similar in humans and nonclinical species.

<sup>c</sup> Tremors were observed in 300 and 450 mg/kg/day female mice in AT-0313-28; however, the incidence of findings was not statistically significant at either dose.

<sup>d</sup> Exposure values at 1000 mg/kg SAM were estimated as follows: Day 1 SAM exposure values in females at 350 mg/kg/day SAM from Study AT-0313-41 were multiplied by a factor of ~2.86 (=1000/350) assuming linear increases in metabolite exposure from 350 to 1000 mg/kg/day SAM

<sup>e</sup> Exposure values were reported from 39-week dog study (AT-0313-19)

[Source: NDA 213378, Nonclinical overview]

**Table 10: Nonclinical to Clinical Exposure Multiples for RDC-9986 and RDC-1066 in Toxicology Studies Relevant to the Safety Assessment of Major Human Metabolites**

Study Type	Study	Dose (High Dose, MTD, or NOAEL) <sup>a</sup>	Sex	RDC-9986/ RDC-1066 AUC (ng*hr/mL) <sup>b</sup>	Nonclinical to Clinical Exposure Multiple of RDC-9986/RDC-1066 at the ALKS 3831 20/10 MRHD (×) <sup>c</sup>
General Toxicity	26-week rat (AT-0313-16)	50 mg/kg/day: high dose and MTD for M; high dose and NOAEL for F	M	12,400/96.2	67/1.6
			F	3620/260	19/4.3
	39-week dog (AT-0313-19)	10 mg/kg/day: high dose and NOAEL	M	11,300/1710	61/28
			F	12,600/1680	68/27
Embryofetal Development	Rat (AT-0313-22)	25 mg/kg/day: NOAEL	F	2620/146	14/2.4
	Rabbit (AT-0313-23)	90 mg/kg/day: high dose and NOEL	F	19,000/27,900	102/457
Carcinogenicity	26-week <i>rasH2</i> Tg mouse (AT-0313-37)	500 mg/kg/day: high dose with no tumor formation	M	96,100/1800	517/29
			F	69,500/4360	374/71
	2-year rat (AT-0313-26)	75 and 60 mg/kg/day in M and F, respectively: high dose with no tumor formation	M	35,400/160	190/2.6
			F	9650/317	52/5.2

Abbreviations: F=female; M=male; MRHD=maximum recommended human dose; MTD=maximum tolerated dose; NOAEL=no-observed-adverse-effect level; NOEL = no-observed-effect level; Tg=transgenic

<sup>a</sup> Per M3(R2) Questions and Answers (International Conference on Harmonisation 2012), Alkermes considers the high dose or MTD to be the appropriate nonclinical endpoint for findings that can be readily monitored in the clinic. The NOAEL may be the most appropriate endpoint for findings that are not readily monitorable. In the chronic general toxicity studies, there either were no adverse findings (39-week dog study) or adverse findings that could be readily monitored clinically (eg, hepatocellular vacuolation with clinical chemistry correlates in the 13-week rat study at ≥75 mg/kg/day). In the EFD studies, increased resorptions and skeletal variations, decreased fetal body weights, and skeletal malformations were the adverse effects in the rat study; these were not considered to be readily monitorable clinically. There were no adverse developmental findings in the rabbit EFD study. In the carcinogenicity studies, there were no treatment-related tumors, indicating the high doses were the appropriate endpoints for comparisons to the MRHD.

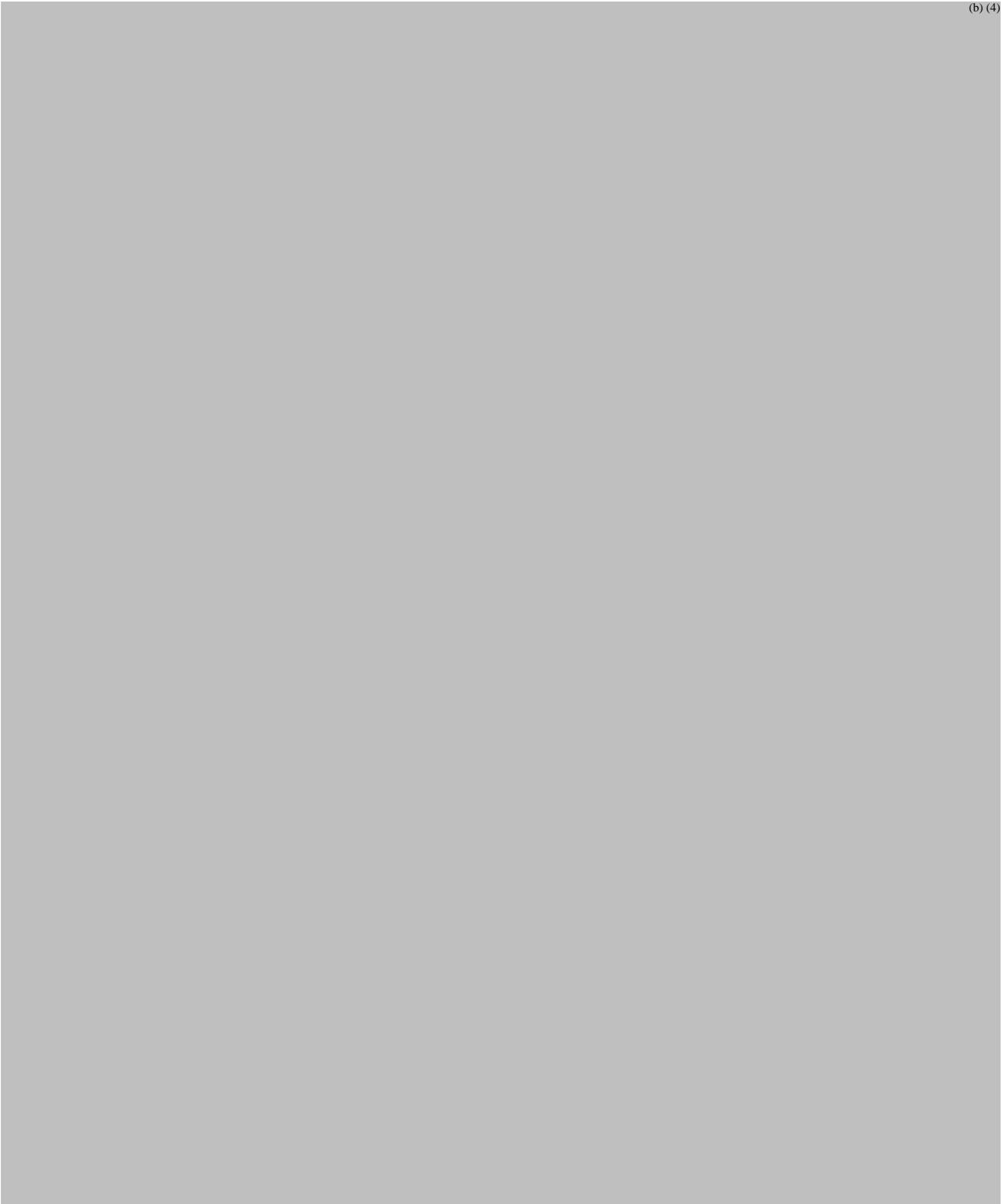
<sup>b</sup> AUC<sub>last</sub> or AUC<sub>0-24h</sub> values at steady state are reported for RDC-9986/RDC-1066 measured in toxicology or bridging toxicokinetic studies in mice (AT-0313-42), rats (AT-0313-41), rabbits (AT-0313-40), and dogs (AT-0313-43); see study reports for details.

<sup>c</sup> Values were calculated by dividing the nonclinical C<sub>max</sub> and AUC exposure values for each analyte by the corresponding clinical steady-state C<sub>max</sub> and AUC exposures from 10 mg SAM (MRHD) following repeated daily oral administration of ALKS 3831 20/10 in Study ALK3831-A104. AUC<sub>24h</sub> of 186 ng\*hr/mL for RDC-9986 and 61.1 ng\*hr/mL for RDC-1066.

[Source: NDA 213378, Toxicology written summary]

## 12 Appendix

### 12.1 ECAC Final study minutes



(b) (4)

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/  
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AMY M AVILA  
07/27/2020 02:53:19 PM

AISAR H ATRAKCHI  
07/27/2020 03:21:37 PM

RICHARD D MELLON  
07/27/2020 05:29:26 PM  
I concur.